From Scrapie to Prion Disease: The Social Construction of a Novel Infectious Agent

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For Jong-mi

Declaration

I declare that this thesis is my own work throughout

12th February 2003
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Abstract

The aim of the research is to examine socio-historically the medical scientific disputes relating to the so-called prion disease including scrapie, bovine spongiform encephalopathy (BSE), transmissible mink encephalopathy (TME), chronic wasting disease, kuru, Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler-Scheinker (GSS) and fatal familial insomnia. BSE and new variant CJD have become the subject of increasing debate and controversy involving many different professional and non-professional groups. Some scientists have launched large projects to examine the nature of the fatal disease since the 1960s by studying a prototype of mad cow disease, scrapie in sheep. While there are many different hypotheses regarding the cause of scrapie, BSE and new variant CJD, currently the majority of scientists accept a hypothesis called "prion theory". Prion theorists claim that the disease is caused by abnormal proteins that contain no DNA, which has long been regarded as the blueprint of every single life form. This theory has held centre stage of the severe controversy, but the scientific community has gradually come to accept the prion hypothesis. However, some researchers still do not agree with this view. To understand these contemporary circumstances necessitate an examination of the history of scientific disputes relating scrapie, and this research will analyse how competing hypotheses have achieved and lost credibility within the scientific community and wider arenas.

This research has three major aims. Firstly, it shows the history of scrapie research in the context of development of biomedicine in the twentieth century. The development of scrapie research corresponded with on-going institutional changes in British and later American biomedicine. Secondly, this research examines the relations between scientific practice and wider social transformations which have been closely associated with the development of scientific knowledge. In particular, the development of molecular biology and biotechnological enterprise has played a vital role in building consensus around so-called prion research. Thirdly, this work builds on an appropriate methodological framework from within the sociologically

informed history of medicine, which has shown that medical scientific knowledge can be analysed in ways similar to the analysis of other social beliefs and knowledge systems. This work aims to contribute to that well-established tradition of social history of science, which refers primarily to the theoretical works of the sociology of scientific knowledge (SSK).

Chapter 1 - Introduction

On 6 October 1997, the Nobel Assembly at the Karolinska Institute announced the award of the Nobel Prize in Physiology or Medicine for 1997 to Stanley Prusiner for his discovery of "Prions – a new biological principle of infection".[1] The Nobel Committee explained that Prusiner had added prions to the list of well-known infectious agents including bacteria, viruses, fungi and parasites. According to Prusiner, a prion is not a virus or a bacterium, but a protein devoid of nucleic acids and RNA. Prions were held to be responsible for a category of diseases that has become known as transmissible spongiform encephalopathies (TSEs) or prion diseases, including scrapie (sheep and goats), bovine spongiform encephalopathy (known as BSE or mad cow disease of cattle), transmissible mink encephalopathy (mink), chronic wasting disease (deer), kuru (humans), Creutzfeldt-Jakob Disease (humans), Gerstmann-Straussler-Scheinker disease (humans) and fatal familial insomnia (humans). After Prusiner suggested his novel theory of infection in *Science* in 1982,[2] the scientific community entered a long period of controversy. The prion theory was denounced by many scientists as "heretical", because it suggested that the agent was proteinaceous in nature; it was therefore seen as a direct challenge to the conventional wisdom of molecular biology, according to which only nucleic acids could embody and transfer information. Subsequently, influential sections of the wider scientific community gradually accepted Prusiner's once heretical idea. Nevertheless, throughout the 1980s and 1990s, the two opposite parties of scientists failed to reach agreement on the meaning of their scientific results.

In this context, the Nobel committee's decision seemed to put an end to the twenty-year controversy. Although the award of the Nobel Prize to Prusiner implied that the scientific community had finally endorsed his idea of the prion, the

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[1] **Karolinska Institute** (1997) 'The Nobel Assembly at the Karolinska Institute has today decided to award the Nobel Prize in Physiology or medicine for 1997 to Stanley B. Prusiner', *Press Release* (6 October 1997)

[2] **Prusiner, S. B.** (1982) 'Novel proteinaceous infectious particles cause scrapie', *Science* **216** (4542): 136-44

endorsement was by no means universal. Prusiner's winning of the Nobel Prize was not enough to change the prion sceptic's mind. The sceptics have claimed that the infectious agent is not a totally new biological entity, and that there is strong evidence that the agent contains conventional genetic information. For two decades, the two opposing camps have launched countless complicated and sophisticated experiments in order to prove their theoretical arguments. Despite impressive experimental accomplishments on the part of each of the two camps, they failed to reach agreement on the nature of the infectious agent. Much about this controversial subject still remains a mystery. Many scientists still believe that fundamental questions about the nature of the infectious agent remain to be answered conclusively.

With the 1985 outbreak of BSE, commonly known as mad cow disease, in the UK, this group of diseases has been in the spotlight of public attention. The BSE outbreak resulted in the slaughter of about two million cattle, and so far 117 people have succumbed to new variant CJD.[3] This climate of urgency focused scientific and public attention on Prusiner's controversial theory. All of sudden, a small and minor scientific endeavour became a major issue in medical and health science. The outbreak of BSE takes centre stage in various accounts of the history of prions and prion diseases, including accounts sociologists and historians of medicine. This should be notable that those sociological and historical approaches on the prion disease had focused mostly on the prion controversy in the period of the post-BSE crisis. In particular, many researchers have dealt either with the role of mass media and government policy in the controversy[4] or with broad overview on mad cow

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[3] **Department of Health** (2002) 'Monthly Creutzfeldt-Jakob disease statistics', *Department of Health* (www.doh.gov.uk/cjd/stats/nov02.htm)

[4] **Ratzan, S. C., ed.** (1998) *The Mad Cow Crisis: Health and the Public Good* (London, UCL Press); **Gregory, Jane and Steve Miller** (1998) *Science in Public: communication, culture and credibility* (Cambridge, Mass: Perseus Publishing); **Adam, Barbara** (2000) 'The media timescapes of BSE news', Stuart Allen, Barbara Adam, and Cynthia Carter (eds) *Environmental Risks and the Media* (London: Routledge): 117-129; **Little, Gavin** (2001) 'BSE and the regulation of risk' *The Modern Law Review 64*: 730-756; **Miller, David** (1999) 'Risk, science, and policy: definitional struggles, information management, media and BSE' *Social Science and Medicine 49*: 1239-1255; **Brookes, Rod** (1999) 'Newspapers and national identity: the BSE/CJD crisis and the British Press' *Media, Culture & Society 21*: 247-263; **Jasanoff, S.** (1997) 'Civilization and madness: the great BSE scare of 1996', *Public Understanding of Science 6*: 221-232; **Seguin, Eve** (2000) 'The UK

disease.[5] By contrast, this research deals much more with matters internal to the scientific research process and community. In other words, the main theme of this research is to show how researcher in this field conducted their experimental projects and struggled to construct hypotheses to order to explain experimental results.

Historically, there are records of what is now considered to be a prion disease in sheep from as far back as 1752. Since the first report of this disease – scrapie - various groups in Britain and on the Continent have tried to elucidate its cause and nature. This thesis begins with the long, and relatively unknown history of research on this mysterious disease. A few words must be said about why the case of scrapie research has been chosen. Although TSE includes at least seven neurodegenerative diseases, and each of them has its own history, there are several reasons why scrapie is significant in this historical study. Firstly, many researchers have regarded the disease in sheep and goats as the prototype of prion diseases in humans and animals. Secondly, it has a long history of research, and from the studies, scientists could make a research model for other diseases. Furthermore, scrapie research is at the crossroads of several disciplines, including biomedicine, veterinary science, virology, genetics, microbiology, biochemistry and molecular biology. For these reasons, it can be said that scrapie research has also encompassed much of modern biology and biomedicine. It provides good resources for understanding current developments in biomedicine, including prion research.

Long before the outbreak of BSE in Britain, a handful of scientists were involved in scrapie research, and had been since the beginning of the twentieth century. However, the research project was quite basic and primitive until the infectious agent was transmitted into laboratory animals in 1961. From that point on, two big research

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BSE crisis: strengths and weaknesses of existing conceptual approaches', *Science and Public Policy 27* (4): 293-302; **Reeves, Carol** (2002) 'An orthodox heresy: scientific rhetoric and the science of prions' *Science Communication 24* (1): 98-122; **Dressel, Kerstin** (2002) *BSE-The new dimension of uncertainty* (Berlin: Edition-Sigma)

[5] **Lacey, Richard** (1994) *Mad cow disease* (Jersey: Cypsela); **Fisher, John R.** (1997) 'Of plagues and veterinarians: BSE in historical perspective', *Argos 16* (2): 225-233; **Fisher, John R.** (1998) 'Cattle plagues past and present: the mystery of mad cow disease', Journal of Contemporary History 33 (2): 215-228; **Rhodes, Richard** (1997) *Deadly Feast: Tracking the Secrets of a Terrifying New Plague*. (New York: Simon & Schuster); **Cooke, J.** (1998) *Cannibals, Cows, and the CJD Catastrophe* (London: Minerva); **Schwartz, Maxime** (2003) *How the cows turned mad* (Berkeley & Los Angeles: University of California Press)

institutes in Scotland and England launched large-scale experimental projects to examine the nature of the disease. To understand the current controversy on mad cow disease and the nature of prion, it is necessary to review how scientists have built up the concept of the disease. The history of scrapie research provides an archetype of current understandings of the nature of the infectious agent of those diseases.

This thesis comprises two parts: the first part will deal with the early history of scrapie research and especially its development in the 1960s and 1970s. During that time, many British scientists constructed various possible models of the nature of the infectious agent. In particular, a group of researchers in the Institute for Research on Animal Diseases (IRAD) at Compton, Berkshire, produced a remarkable result, i.e. that the scrapie agent resisted radiation treatments. From this experiment, the researchers suggested that the agent did not contain nucleic acids, which have been thought of as carrying the blue print of all life forms on earth. At the time, scientists believed that every nucleic acid-containing organism should be inactivated by radiation treatment. However, the scrapie agent was not inactivated by such treatment. This could be read as evidence for the absence of nucleic acids. In contrast, at the same time, a collaborative research team in the Moredun Research Institute and Animal Breeding Research Organisation (ABRO) in Edinburgh claimed on the basis of a series of genetic and pathogenetic experiments that although the infectious agent was very small and had other anomalous properties, nevertheless there was strong evidence to show that it did in fact have an informational molecule. This opposing speculation caused a controversy between the two camps during the 1970s. The two groups of scientists clashed at various conferences and official meetings. The dispute was not resolved at the time. Instead, the scientific confrontation was brought to an end not by decisive scientific evidence, but by the intervention of a governing body, the Agricultural Research Council (ARC). Consequently, this section of my study of scrapie research mainly endeavours to show how divergent positions within the controversy were sustained by differences of institutional traditions and their research cultures and to elucidate the political circumstances that led to the closure of the dispute.

The second part deals with scrapie research in the 1980s and 1990s. In particular, the prion controversy will be the central issue in this part. In 1982, Prusiner's suggestion of the proteinaceous nature of the agent (implying that the agent might consist of nothing but protein) caused a long battle between the prion group and its sceptics. The present study will describe how Prusiner, at that time an unknown neurologist in San Francisco, formulated the novel idea, which caused such a controversy in the scientific community, and that came to public prominence with the outbreak of mad cow disease in Britain. This part of the thesis will also endeavour to answer the question: how did the prion theory become the mainstream idea in the field of scrapie research? When Prusiner first put forward his theory in 1982, most scrapie researchers dismissed it as heretical. However, within 20 years he had gained considerable scientific credibility from fellow scientists and the general public. Correspondingly, his opponents, the prion sceptics, who were once the mainstream in this field, had been marginalised. Nevertheless, the two groups continued to pursue their own research project. For the last twenty years, the opposing stances have not come to any point of agreement. Although there is a propensity from time to time for each side to claim to have arrived at so-called crucial experimental results, the data invariably turn out to be flexible and open to interpretation. To explain this controversy and its outcome, the present study considers some situational elements which play a role both in sustaining local disagreement and in catalysing the process of consensus-building amongst a wider constituency of fellow scientists and the public. A wide array of factors is involved, ranging from personal characteristics to structural changes in the social circumstances surrounding scientific practice. In this study, particular emphasis will be placed on some social elements which can be seen to be involved in explaining the controversy.

Running through the two parts of the thesis will be three predominant themes. The first examines the history of scrapie research in the context of development of biomedicine in the twentieth century. As I will show, the development of scrapie research corresponded with on-going institutional changes in British and later American biomedicine. Scrapie research was initially established through the

development of veterinary medicine in Britain. The subject went onto the main research agenda with the establishment of the Agricultural Research Council (ARC). The early scientific debates between British researchers were deeply implicated in the institutional restructuring of the ARC in the 1970s. Similarly, from the 1970s, the prion controversy was equally deeply implicated in the changing culture of American biomedical research. It is notable that the scrapie research can be located in the context of the development of biomedicine in the twentieth century.

Secondly, this study of the controversy will examine the relations between scientific practice and wider social transformations which have been closely associated with the development of scientific knowledge. In particular, the development of molecular biology and biotechnological enterprise has played a vital role in building consensus around so-called prion research. Other historians have argued that the development of molecular biology and its related technologies is closely associated with wider social transformations after World War II.[6] This co-development of scientific practice and wider social transformation is called "molecularisation". The present study will show not only how the scientific practice of prion research has been strongly influenced by this scientific and social transformation, but also that the consensus-building process has been affected by the same wider scientific-social transformation.

Thirdly, the present study aims to contribute to that well-established tradition of social history of science which refers primarily to the theoretical works of the

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[6] **Wright, Susan** (1986a) 'Recombinant DNA technology and its social transformation, 1972-1982', *Osiris 2*: 303-360; **Wright, Susan** (1993) 'The social wrap of science: writing the history of genetic engineering policy', *Science, Technology and Human Values 18*: 79-101; **Wright, Susan** (1994) Molecular Politics: developing American and British regulatory policy for genetic engineering (Chicago: University of Chicago Press); **Wright, Susan** (1998) 'Molecular politics in a global economy', Arnold Thackray (ed.) *Private Science: biotechnology and the rise of the molecular sciences* (Philadelphia: University of Pennsylvania Press): 80-104; **Kay, Lily E.** (1992) The *Molecular Vision of Life: Caltech, the Rockefeller Foundation and the Rise of the New Biology* (Oxford: Oxford University Press); **Kay, Lily E.** (1998) 'Problematizing basic research in molecular biology', Arnold Thackray (ed.) *Private Science: biotechnology and the rise of the molecular sciences* (Philadelphia: University of Pennsylvania Press): 20-38; **Kay, Lily E.** (2000) Who Wrote the Book of Life? A history of the genetic code (Stanford, California: Stanford University Press); **De Chadarevian, Soraya & Harmke Kamminga** (eds) (1998) M*olecularising Biology and Medicine: new practice and alliances, 1910s-1970s* (London: Harwood Academic Publisher); **De Chadarevian, Soraya** (2002) *Designs for life: molecular biology after World War II* (Cambridge: Cambridge University Press)

sociology of scientific knowledge (SSK).[7] This study is informed by current concerns in SSK, and among its purposes is that of strengthening the historiographic value of examining the causal connection between socio-cultural conditions and the production of scientific knowledge. This study shows how the clash between different institutional traditions and cultures in America and Britain has shaped the production of knowledge on scrapie. In particular, it shows how views on the nature of the infectious agent are based upon differently patterned laboratory cultures and different styles of scientific practice. I will show that these different styles were embodied in particular patterns of scientific practice, including the formulation of hypotheses, and the conduct, interpretation, and presentation of experiments.

Furthermore, it is worth noting that the present study may provide a good empirical example in support of history of science that draws on SSK, namely sociologically informed history of science. This study is based upon sociological methods that are informed by SSK. One of the tenets of SSK in particular - symmetrical social analysis of all knowledge, irrespective of our current evaluations of its truth or its adequacy – offers a sound methodological approach for explaining scientific practice. According to David Bloor, the same types of cause would explain true and false beliefs.[8] In other words, we should apply the same general explanatory framework to analyse the generation and reception of both "true" and "false" knowledge. [9] This sociological analysis encompasses all scientific knowledge, including "right" knowledge as well as scientific knowledge now regarded as

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[7] The sociology of scientific knowledge is a sociological, historical and philosophical movement in science studies since the early 1970s. In their studies of the social construction of scientific knowledge, the authors looked at the social and cultural contingencies under which knowledge claims are produced. In particular, this relativist movement suggests that both true and false beliefs should be treated and explained symmetrically. For details, see **Bloor, David** (1991) *Knowledge and Social Imagery* (Chicago: University of Chicago Press), **Barnes, Barry & Bloor, David** (1982) 'Relativism, rationalism and the sociology of knowledge' Martin Hollis & Steve Lukes (eds) *Rationality and Relativism* (Oxford: Blackwell): 21-47; **Shapin, Steven and Simon Schaffer** (1985) *Leviathan and the Air-pump: Hobbes, Boyle, and the experimental life* (Princeton, New Jersey: Princeton University Press); **Barnes, Barry, Bloor, David & Henry, John** (1996) *Scientific Knowledge; a sociological analysis* (London: Athlone); **Bloor, David** (2001) 'What is a social construct?' *Facta Philosophica* 3: 141-156

[8] **Bloor, David** (1991) *op. cit.* note 7: 7

[9] **MacKenzie, Donald** (1996) *Knowing Machines: essays on technical change* (Cambridge, Mass: MIT Press): 10

inadequate. It is a methodological tenet that has been applied to good effect in this empirical case. From the 1970s on, there were two big disputes on the nature of the infectious agent. At each stage of development, consensus has been built differently. In other words, a theoretical argument regarded as "true" knowledge in the 1970s was later found wanting and was discarded. Throughout the prion controversy, previously dominant knowledge became marginalised and regarded as inadequate knowledge.[10] In the context of this study, symmetrical analysis can provide a vital methodological principle for analysing the history of scrapie research.

Materials and methods

This thesis has employed a variety of research methods. It is part historical reconstruction of events using documents and interviews, and part sociological analysis of scientists' practice and controversy. I examined what scientists have reported about their research activities in formal reports (articles, graphs, statements made at conferences, textbooks, and so forth). The materials range from articles in the *Journal* of Parliament in 1752 to the current issues of *Nature* and *Science*. I have read at least 1,700 scientific journal articles, books, statements, personal communication letters, conference proceedings, meeting notes, minutes of council meetings (including the Agricultural Council and Medical Research Council) and witness statements of the BSE Inquiry. I also read newspaper accounts of scrapie research to assess the kinds of information reaching the general public. These have been the basic materials for my reconstruction of scientists' work activities.

I interviewed twenty prominent scrapie researchers both in Britain and America about their different experimental experiences and perspectives on the subject of scrapie research. I did most interviews and much of the fieldwork for observation of laboratories between 2000 and 2001. I visited several main scrapie research centres in Britain and America including the Neuropathogenesis Unit (Edinburgh), the Institute

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[10] For more detailed discuss on the issue of relativism and symmetry, see **Bloor, David** (1984) 'The strengths of the strong programme', James Robert Brown (ed.) *Scientific Rationality: the sociological turn* (Dordrecht: D. Reidel Publishing): 75-94; **Collins, H.M.** (1996) 'In praise of

for Research on Animal Diseases (Compton, England), the Institute for Basic Research (New York), the Maclaughlin Institute (Great Falls, Montana), the Rocky Mountain Laboratory of the National Institutes of Health (Hamilton, Montana), and the Institute for Neurodegenerative Diseases (University of California, San Francisco). In a series of interviews, I was able to talk to leading researchers, postdoctoral researchers, technicians and administrators of scrapie research institutes.

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futile gestures: how scientific is the sociology of scientific knowledge?' *Social Studies of Science* 26: 229-244

Chapter 2 - Background history of scrapie research in Britain, 1750-1960

1. Introduction

Scrapie has a long history in Britain. It has only been in the spotlight since the 1980s, when the mass media brought it to public attention in connection with the concerns over mad cow disease, but, arguably, it actually dates back to the eighteenth century. For two centuries, agricultural industry suffered serious economic losses due to several large-scale outbreaks of what, with the benefit of hindsight, we can identify as scrapie. Of course, considerable difficulties attend any attempt retrospectively to diagnose historical occurrences of a disease using modern categories. I shall not try to address the profound epistemological and methodological issues generated by this problem because the focus of my concerns lies elsewhere. Nevertheless some mention must be made of the principles that underlie the use of the word "scrapie" in the brief historical survey that I want to give. It seems plausible to suppose that the farmers and shepherds who dealt with sheep on a day to day basis would have been keen and intelligent observers of their behaviour and would be well able to identify unusual patterns of behaviour and the symptoms of a number of forms of pathology, especially if these symptoms were dramatic and manifested themselves in grossly unusual forms of behaviour. It is also reasonable to assume that these observable symptoms will often have fallen into clusters, though these will have been rather variable and rough and ready. For obvious reasons, the names given to these descriptions of the symptom clusters will themselves have been very varied and localised, though the descriptions of the clusters themselves (using common, everyday language) will show some recognisable continuities. On this basis I will allow myself to speak retrospectively of "scrapie-like" diseases that have plagued farmers for many years. Although we should exercise great caution here, for the sake of brevity, we may allow ourselves to think of scrapie "itself" (that is, as an underlying cause or nexus of causes) as having

been present for at least two centuries. This seems a reasonable way of making sense of the reports of the last two hundred years, at least as judged by the descriptions given in those records. I shall now survey these records and treat them as *prima facie* responses to the occurrence of a scrapie-like phenomenon, with all the above-mentioned qualifications taken for granted.

In this chapter, I shall review the early history of scrapie epidemics and research on scrapie by some pioneering veterinary scientists. I will then show that the growth of scientific research on scrapie has been closely associated with the institutionalisation of veterinary and agricultural science, particularly in Britain. In particular, two historically important events were crucial for scrapie research: the establishment of the Moredun Institute, and the creation of the Agricultural Research Council (ARC). The former was the one of the first private-funded agricultural research institutes in the 1920s, and the latter was established as the government support organisation for agricultural research in the 1930s. Both institutions played an important part in developing and institutionalising scrapie research, which had been largely dependent on folk knowledge up until then. Scrapie research became an important research subject within veterinary science, and during the 1930s and 1940s, a variety of experimental projects brought about the basic understanding of scrapie. Subsequently, with the international outbreaks of scrapie in the 1950s, the Agricultural Research Council decided to set up large-scale scrapie research programmes in Edinburgh and Compton. The Moredun Institute in collaboration with the Animal Breeding Research Organisation built up a joint research unit to conduct genetic research in Edinburgh. In addition, another biochemical research project was launched at the Institute for Research on Animal Disease in Compton. These programmes were the first intensive large-scale research on scrapie in Britain, and this was to bear fruit in the 1960s.

2. The first prevalence of scrapie in Britain: 1730-1820

The earliest written record of scrapie in England dates from the 1750s. This account of the disease was given in the *Journal of the House of Commons.* Farmers in

Boston, Lincolnshire, sought to restrain "jobbers" from mixing healthy sheep with distempered animals and reselling them. At the time, the "jobbers" had a monopoly of the sheep trade in Britain. In the decade 1745-1755, the distemper ravaged many farms in Lincolnshire, and farmers and sheep breeders began to recognise that epidemics of the disease were causing huge financial losses. Hence, in 1754, the farmers drafted a petition to the House of Commons, in which the distemper in question was referred to as "rickets" or "shakings".[1] The House of Commons appointed a special committee to investigate this problem.[2]

Subsequent writers traced the origins of the disease somewhat earlier. According to Thomas Comber in 1772, a distemper called "rickets" had been known for forty years in Lincolnshire. He outlined the symptoms of the disease and its existence in the 1730s:

> The principal symptoms of the first stage of this distemper is a kind of high headedness. The affected sheep appear much wilder than usual. He bounced up suddenly from his laire and runs to a distance as though he were pursued by dogs. In the second stage the principal symptom of the sheep is his rubbing himself against trees, posts, & c., with such fury as to pull off his wool and tear away his flesh. The distressed animal has now a violent itching of the skin...but it does not appear that there is ever any cutaneous eruption or salutary critical discharge. The third and last stage...the poor animal appears stupid, separates from the flock, walks irregularly (whence rickets), generally lies, and eats little. These symptoms increase in degree till death follows a general consumption, which appears upon dissection of the carcass, the juices or even solids having suffered a general dissolution insomuch that the solids have no longer any of the good properties of flesh, nor the blood of its usual colour...not any precise time from first symptom to death,...I do not find that this distemper is infectious, but hereditary equally from sire and dam; and may be latent one generation and reappear. A sheep once attacked never recovers; escaping it in early years, never takes it...**The disease was about forty years standing in England; came from Lincolnshire hither,** and yet I have never heard of the distemper in our country (Yorkshire).[3]

His description reveals that the disease was understood to have originated in Lincolnshire in the 1730s, where it was known as rickets or shakings. The sheep

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[1] **House of Commons** (1755) *Journal*: 27, 87, & 164-183; **Parry, Herbert B** (1983) *Scrapie Disease in Sheep* (London: Academic Press): 37

[2] **Select Committee** (1755) 'Report from the Select Committee on the petition of several breeders and feeders of sheep in the county of Lincoln', *Report of the Select Committees, First Series. XI*: 379

[3] **Comber, Thomas** (1772) *Real Improvements in Agriculture: Letters to Reade Peacock, Esq. and to Dr. Hunter, Physician in York, concerning the Rickets in Sheep* (London: print for W. Nicoll): 8

affected by this scrapie-like disease showed several symptoms: sensitive reactions, dizziness, itchiness, and paralysis of the body. The author believed that it was a hereditary disease, not an infectious one. A similar disease was noted in Wiltshire in the 1750s, and was severe from 1770 to 1810.[4] The disease in Wiltshire went under the name of goggles, and several authors identified the goggles with the rickets in Lincolnshire. An anonymous writer, a Gentleman in Wiltshire, wrote a remarkably clinical and pathological description of the goggles in his letter to the Bath and West of England Society:

> Gentlemen,
> Within these few years, we have had a disease among the sheep, now generally known by the name of the goggles; a disease which has destroyed some in every flock round this county, and made great havock in many. [...] it is not infectious, but hereditary, and undoubtedly runs in blood. It has no affinity with giddiness, for they do not run around. It most resembles the staggers in lambs, with this difference that whereas staggery lambs, show weakness before, and fall forward, goggle sheep show a weakness behind, and fall backward, when forced to run. When first observed to be diseased, their ears drop, and they rub their tails much more than other sheep; they then discover the weakness above mentioned, and grow poorer and weaker till they cannot drag their limbs behind them, and at length die. I have examined a few and found the viscera all round. I have blooded one, and found no inflammatory crust. I can neither myself imagine, nor find one who can venture even to conjecture, the cause. As it is a matter of consequence, perhaps, were you to make it the subject of the two following premiums, it might be a means of stopping its progress: the first, to the surgeon who shall dissect the greatest number of goggly sheep, and give the most accurate description, with the best observations on the disease; and the second, to the person who shall discover an effectual cure.
> I am, Gentlemen, & c.[5]

The symptoms of goggles in Wiltshire, as described in this letter, were similar to rickets in Lincolnshire. An epidemic of scrapie-like disease also occurred in the Dorset area by the 1780s. According to John Claridge of Craig's Court:

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[4] **Davis, Thomas of Longleat** (1795) 'Extracts from a General View of the Agriculture of the County of Wiltshire: with observations on the means of its improvement: drawn up for the consideration of the Board of Agriculture and internal improvement', *Letters and Papers on Agriculture: Bath and West of England Society 7*: 113-221; **Collins, J.** (1799) 'Some further practical remarks on the nature of sheep and wool and the disorders of sheep', *Letters and Papers on Agriculture: Bath and West of England Society 9*: 113-128

[5] **Gentleman of Wiltshire** (1777) 'On the disease called the Goggles in sheep', *Letters and Papers on Agriculture: Bath and West of England Society 1*: 42-44

> It is incumbent on me to take notice of a disorder peculiar to sheep, which is sometimes fatally experienced in this county, called the Goggles; it attacks them at all ages, and no remedy is at present known for it. [...] And this disorder has been known to be fatal to the greatest part of flock.[6]

By the early nineteenth century, many documents testify to the fact that between the 1770s and 1810s there was a severe epidemic of the disease. From these records, the disease was prevalent in much of southern England (Dorset, East Anglia, Lincolnshire, Devonshire, Oxfordshire, Cambridgeshire and so forth) under the names of rickets, goggles and rubbers. Many farmers and landowners lost their flocks within a few years, and it resulted in serious economic losses in these regions.

However, by the 1810s, this epidemic was gradually abating. Many authors in a series surveying agriculture in the various English counties referred to its decline between 1795 and 1813, when the disease gave less cause for concern in Dorset, Hampshire, Oxfordshire, Berkshire, Bedfordshire and Wiltshire.[7] Although the severity of the epidemic in England declined from the 1830s, it continued to spread; the disease reached as far as the Border area of Scotland in the mid-1800s. Records of the Borders and Southern Scotland revealed that around 1853 some farmers reported its existence under the name, "scrapie".[8] The outbreak of the disease in the Borders area appears to be the first to be given that name. John Cameron in Northumberland gave another account of the outbreak in the Borders area:

> The disease was well known on certain farms in Northumberland and Roxburghshire sixty years ago [1850s], it may be noted in passing that at the present day [1910s] in

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[6] **Claridge, John, of Craig's Court** (1795) 'Extracts from a General View of the Agriculture of the County of Dorset: with Observations on the means of its improvement', *Letters and Papers on Agriculture: Bath and West England Society 7*: 72-73

[7] **Stevenson, W.** (1812) *General View of the Agriculture of the County of Dorset* (London); **Vancouver, Charles** (1813) *General View of the Agriculture of the County of Hampshire including the Isle of Wright* (London); **Vancouver, Charles** (1808) *General View of the Agriculture of the County of Devon; with Observations on the means of its improvement* (London: printed for Richard Phillips); **Young, Arthur** (1813) *General View of the Agriculture of Oxfordshire* (London); **Cleeve, Henry** (1840) 'Practical essay on disease of sheep', *Journal of the Royal Agricultural Society of England 1*:295-345

[8] **Stockman, Stewart** (1913) 'Scrapie: an obscure disease of sheep', *Journal of Comparative Pathology and Therapeutics 26*: 317-327

Roxburghshire the disease is known by such further names as "scratchie" and "Cuddie Trot."[9]

To sum up, since the 1750s a severe epidemic of a scrapie-like disease had spread from southern England and reached right into Scotland by the 1850s. It became less prevalent from the 1830s and in England the disease disappeared. The virulence or at least the economic significance of the disease appeared by that time to have been on the decline. With its decline, the disease generally received no more than passing mention, alongside other diseases of sheep.

Author/Year	Causes of Scrapie	Reference
T. Comber (1772)	Hereditary	"I do not find that this distemper is infectious, but hereditary equally from sire and dam"
Gentleman of Wiltshire (1777)	Hereditary	"it is not infectious, but hereditary, and undoubtedly runs in blood."
J. Claridge (1795)	Hereditary	"some of the old-fashioned farmers think that, as no such disease existed prior to the introduction of the breed from other countries, consequently its origin may be imputed to this cause"
A. Young (1800)	Hereditary (?)	"The Spaniards did worst, next the new Leicesters, and the Southdowns much the best"
A.F.M. Willich[10] (1802)	Hereditary	"The rickets appear in the spring, and are hereditary"
C. Vancouver[11] (1811)	Infectious	"moreover, as this disorder is considered to be infectious, the sheep are usually killed on the appearance of the first symptom"
W. Stevenson[12] (1815)	Infectious or Hereditary	"The disorder is believed to be infectious or hereditary, and a medical gentleman attempted in vain to discover the cause"
W. Humfrey[13] (1840)	Infectious	"I am of opinion that this disease is infectious"

Table 1: Concepts of scrapie aetiology (1750-1850)

[9] **Cameron, John** (1913) 'Vide lecture to Northumberland Shepherds', Society at Ancroft, Northumberland' *Berwick News* (13 February, 1913): 6

[10] **Willich, A. F. M.** (1802) *Domestic Encyclopaedia* (London: printed for Murray and Highley) Vol. III: 495

[11] **Vancouver, Charles** (1811) *General View of the Agriculture of the County of Cambridge* (London): 276

[12] **Stevenson, W.** (1815) *General View of the Agriculture of the County of Dorsetshire* (London): 416-417

[13] **Humfrey, W., of Boxford** (1840) 'Footnote to Cleeve's practical essay in disease of sheep', *Journal of the Royal Agricultural Society of England 1*: 297

As seen in the writings mentioned above, the disease was called by different names, but they all encompassed much the same symptoms: dizziness, nervousness, rubbing, losing wool, paralysis, and so forth. Some writers also conducted relatively simple pathological examinations, but they could find no specific features of the disease.[14] Opinion as to the cause of the disease also varied. Initially, many assumed that it might be hereditary. The belief that "scrapie" was hereditary in character was dominant in the earlier writings in the mid-eighteenth century. In the early nineteenth century, opinion gradually changed, and it was thought that "scrapie" might be an infectious disease.

As seen in the table, it is notable that aetiological accounts of the disease now identified as scrapie, i.e., rickets, goggles, varied from one author to another, although we can discern something of a shift in attribution over time. Initially, opinion on the cause of the disease was assumed to be hereditary, introduced in the bloodlines of imported sheep from the Continent. As a Gentleman of Wiltshire argued in 1788, it was widely held that the disease had been found in imported sheep. It was imported sheep from Spain and Saxony (mostly the Merino sheep) that were blamed for causing the disease. In this period, many thought that scrapie might be a hereditary disease rather than an infection. John Claridge of Craig's Court says, "it is very difficult to assign the cause of the disorder [goggles]; but some of the old-fashioned farmers think that, as no such disease existed prior to the introduction of the breed from other countries, consequently its origin may be imputed to this cause; but this is an argument perhaps of prejudice, grounded merely on conjecture, tho' I own I am inclined to give it some credit".[15] A plausible explanation for this change was that when new fine-wooled sheep were introduced in England, and coincidentally the disease spread through the same region, farmers and shepherds might naturally assume that the disease was linked to the newly introduced sheep.[16]

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[14] **A Gentleman of Wiltshire** (1777) *op. cit.* note 5; **Cleeve, Henry** (1840) *op. cit.* note 7

[15] **Claridge, John, of Craig's Court** (1795) *op. cit.* note 6: 73

[16] Many early writings speculated that the origin of the disease was attributed to the importation of Merino sheep from the Continent. Though the first large scale importation of Merino sheep was recorded around 1788 [**Carter, H.B.** (1964) *His Majesty's Spanish Flock: Sir Joseph Banks and the Merinos of George III of England* (London: Angus and Robertson)], there were earlier cases of importation of Merino sheep from the Continent to England

Still, some experts believed that the first prevalence of scrapie in Britain was more than likely due to the introduction of the Merino sheep from the Continent.[17] It later became more common to suppose that the disease was infectious.

It is also important to note that the knowledge of the disease was based on the local wisdom of farmers and shepherds. Prior to the eighteenth century, knowledge of diseases of farm animals was largely local in character, embodied in the craft knowledge and practices of local shepherds and stockmen. The records in which we can identify scrapie were no exception. In this period in Britain, the so-called enlightened gentry wrote most reports on scrapie, but the main source of the records was the local farmers and shepherds. This is apparent in local variations both in how the disease was described and in the names it was given. In the early nineteenth century, there were some agricultural surveys to identify a wide range of different and often locally-defined diseases of sheep.[18] The agricultural surveys did not use the concept of scrapie. Instead, authors focused on what we can see as scrapie-like diseases, such as scab, turnsick, and sturdy. Many of these diseases, as well as rickets and goggles as already mentioned, included some or all of the symptoms that are now taken as diagnostic of scrapie. In the local context, people observed and named the disease in terms of specific manifested symptoms, for instance paralysis of the hind quarters (rickets, or turnsick), dizziness and blindness (goggles or sturdy), and violent itching (rubbers, scratching, or scab).

It is also important to note that diversity of disease taxonomy and of aetiological explanation persisted throughout the nineteenth century, despite efforts to survey and standardise agricultural knowledge. For instance, in the work of John H. Steel,

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[**Walsingham, Thomas** (1937) *St. Albans Chronicle 1406-1420* (Oxford: Clarendon); **Trow-Smith, Robert** (1957) *A History of British Livestock Husbandry to 1700* (London: RKP): 112-113]. From those records of early importation, the correlation between the Merino sheep and scrapie seems to be unlikely. However, the suspicions of farmers and shepherds that the Merino sheep was the culprit were plausible, because in the early 1840s, there was an outbreak of sheep-pox in Britain. Veterinary scientists discovered that the outbreak of the sheep-pox was linked to the Merino sheep, which were imported from Saxony. The Merino sheep was a likely object of suspicion as the cause of a new disease at the time [**Pattison, Iain** (1984) *The British Veterinary Profession 1791-1948* (London: J.A. Allen): 36]

[17] **Parry, Herbert B.** (1983) *op. cit.* note 1

[18] **Youatt, William** (1837) *Sheep: Their Breeds, Management and Diseases* (London: Robert Baldwin); **Spooner, W. C.** (1844) *History, Structure, Economy and Disease of Sheep* (London)

the goggles was categorised as one of the symptoms of turnsick, and rickets was included as a symptom of louping-ill.[19]

3. The first veterinarian research on scrapie

At the turn of the twentieth century, with establishment of the veterinarian profession in Britain, veterinarians began to recognise "scrapie" as a quite distinctive disease entity. Since the year 1853, there had been another big epidemic of scrapie-like disease in the Scottish Borders. Farmers in this area suffered huge economic losses, thanks to new outbreaks. As the epidemic grew worse, farmers began to talk about the disease openly, stimulating an initiative for scientists to continue their investigation. In 1913, Stewart Stockman, the Chief Veterinary Officer (CVO) of the Board of Agriculture, noted the increase in the disease, which he said "probably explains the partial abandonment of secrecy."[20] Thus, scrapie became an important issue amongst veterinarians and farmers.

Research undertaken at the time would largely define the disease, as we now know it, at least in terms of its detailed symptomatic and pathological presentation. The term "scrape" or "scrapie" was a popular name used by farmers when referring to the distemper in southern Scotland. In 1913, Stewart Stockman gave a lecture on scrapie and published it in the *Journal of Comparative Pathology and Therapeutics*.[21] Stockman had studied and taught veterinary pathology and bacteriology in Edinburgh, hence his knowledge of the disease locally called scrapie, which has been recognised as a serious problem in the Borders area since the 1850s.[22] With John McFadyean,[23] who was regarded as a founding father of modern British veterinary

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[19] **Steel, John Henry** (1890) *A Treatise on the Disease of the Sheep* (London: Longman)

[20] **Stockman, Stewart** (1913) *op. cit.* note 8: 317

[21] **Stockman, Stewart** (1913) *op. cit.* note 8

[22] **Pattison, Iain** (1984) *The British Veterinary Professon 1791-1948* (London: J.A. Allen): 110-111

[23] John McFadyean played a significant role in establishing the veterinary profession in Britain. He taught first at the Veterinary College in Edinburgh, then moved to the London Veterinary School. He was a dean and professor of pathology and bacteriology at the London School, and set up one of the first veterinary laboratories for veterinary diagnosis and research in 1892. In 1894, he became principal of the oldest and largest British veterinary school. According to Iain Pattison, "he was the most experienced veterinary pathologist in the country, personally directing a unique laboratory. He owned and edited one of the world's outstanding veterinary research journals, *Journal of Comparative Pathology and Therapeutics*, and

science, Stockman was an advocate of the professionalisation of veterinary medicine, and particularly of the development of a scientific model of professional knowledge and practice. His review on scrapie identified the disease as an appropriate site to develop this model through research, specifically he suggests that the disease is an obscure disease of sheep, and could well be infectious.

Stockman's review raised the profile of scrapie as a serious threat for the agricultural industry at the time. For this reason, scrapie was one of the urgent subjects of investigation on the list of the first government-funded research into animal diseases. When the Development Commission was established under the Development and Road Improvement Funds Act in 1909,[24] John McFadyean, who was the Principal of London Veterinary College, tapped this source for the benefit of the London veterinary school; the sum involved was £1,300, for studies on bovine tuberculosis (£650), scrapie disease of sheep (£230), Johne's disease of cattle (£210), and toxicity of the salts of zinc (£100).[25] From the record of the allocation of research funds, we can see that scrapie was regarded as one of the research priorities. Presumably, it was due to Stockman's influence as a CVO to the Board of Agriculture that funds were earmarked for scrapie. Thanks to the funds, Stockman could launch a series of scientific researches on transmission, starting from the supposition that scrapie was an infectious disease.

Around the same time, a veterinary researcher from the Royal College of Physicians' Laboratory at Edinburgh, John Pool McGowan, published a book, *Investigation into the Disease of Sheep called "Scrapie"*.[26] In his book McGowan claimed that scrapie was caused by heavy infection with *Sarcosporidia* parasites which encyst

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he was privy to the deliberations of the ruling council of the profession." [**Pattison, Iain** (1984) *op. cit.* note 22: 128]

[24] **Henderson, William** (1981) 'British agricultural research and the Agricultural Research Council: a personal historical account', G.W. Cooke (ed.) *Agricultural Research 1931-1981: A History of the Agricultural Research Council* (London: Agricultural Research Council): 8. The Commission's function was to advise the Treasury on making grants or loans for the development of rural and coastal areas, including grants for agricultural research. The Act had significant implications for the establishment of veterinary science and agricultural research. This was the first ever Government grant for veterinary research.

[25] *Ibid.*, 150

[26] **McGowan, J.P.** (1914) *Investigation into the Disease of Sheep called "Scrapie"* (Edinburgh: William Blackwood and Sons)

in the muscle tissues of mammals. When McGowan conducted pathological examinations and inoculation experiments with sheep suffering from scrapie, he observed an interesting feature: the sarcocyst were always presents in large numbers in the skeletal muscles of scrapie sheep. The sarcocyst parasite usually causes severe itchiness in the host. With respect to this symptom, McGowan inoculated sarcosporidial emulsions into rabbits, and reported that this induced the chief symptom of scrapie, pruritus (or itching).[27] From his investigation, he concluded that scrapie was caused by sarcocyst parasite infection. Moreover, he speculated that this parasite infection was not transmitted by physical contacts between sheep; rather, the infection was transmitted from mother to the lamb through the uterine wall. In addition, it could also be transmitted through the milk of diseased animals.[28] This maternal transmission implied that the disease was non-contagious, hereditary, and congenital.

The idea of parasite infection met with strong criticism; one of the leading veterinary scientists at the time, John McFadyean, published his objection to the parasite theory of McGowan in 1918.[29] McFadyean criticised McGowan on the grounds that the latter's argument was based on assumptions which were unproved and improbable. McFadyean's criticims were three-fold: first, scrapie was, to his mind, a contagious disease. According to the description of Stewart Stockman in 1913, there were several cases of contagious infection when sheep shared the same pasture.[30] Second, whereas McGowan claimed that scrapie arose *de novo*, and was not the consequence of infection from a previous case of the disease (i.e., scrapie was caused by spontaneous generation),[31]McFadyean pointed out that the speculation of spontaneous generation was based on a misunderstanding. This mistake came about as a result of the fact that the incubation period of scrapie was remarkably long. McFadyean conducted experiments on transmission for seven years, and concluded

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[27] *Ibid.*, 110

[28] *Ibid.*, 101-109

[29] **McFadyean, John** (1918) 'Scrapie', *Journal of Comparative Pathology and Therapeutics 31*: 102-131

[30] **Stockman, Stewart** (1913) *op. cit.* note 8

[31] **McGowan, J.P.** (1918) 'Scrapie', *Journal of Comparative Pathology and Therapeutics 31:* 278-290

that scrapie had a very long incubation period.[32] Third, if the disease was caused by parasite infection, then scrapie should occur anywhere the parasites were distributed. McFadyean asserted that "in explanation of the fact that scrapie has disappeared throughout nearly the whole of England, although sarcosporidia remain in every flock and are present in the majority of individual sheep, he [McGowan] has nothing serious to offer."[33]

The debate between McGowan and McFadyean was intensified in the *Journal of Comparative Pathology and Therapeutics* in 1918. This controversy was all about the issue of how to understand the unprecedented disease in terms of the germ theory, which had become the newly established framework of biomedicine since the late nineteenth century. On the one hand, McGowan believed that the main candidate for the cause of the scrapie infection was congenital and hereditary infection with the *Sarcocystis* parasite. On the other hand, McFadyean, who was a frontrunner of bacteriology, believed that the disease could be attributed to contagious agent. The debate came to an end with McGowan's parasite theory being abandoned, because scrapie was observed to occur in animals where there was no sarcocystis. To investigate the validity of McGowan's theory, Stockman launched a large-scale programme of pathological and transmission experiments between 1921 and 1926. From this series of experiments, Stockman had observed that when scrapie-affected muscle extracts supposed to contain sarcocystis parasites were injected into normal sheep, no apparent symptoms of scrapie were produced. This experimental result underpinned McFadyean's speculations.[34] Thus, the newly emerging bacteriological explanation was confirmed by the work of McFadyean and Stockman, and played a part in the abandoning of McGowan's parasitological approach.

Arising from the dispute between McGowan and McFadyean in 1918, one significant fact was observed: namely, the incubation period of scrapie seemed to be

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[32] His experimental work was conducted between 1911 and 1918 at the London Veterinary College. See **McFadyean, John** (1918) *op. cit.* note 29: 121-131.

[33] **McFadyean, John** (1918) 'Sarcosporidia as the cause of scrapie', *Journal of Comparative Pathology and Therapeutics 31*: 293

[34] **Stockman, Stewart** (1926) 'Contribution to the study of the disease known as scrapie', *Journal of Comparative Pathology and Scrapie 39*: 42-71

very long.[35] During the 1910s and 1920s, scientists in both Britain and the Continent attempted to uncover the mysterious characteristics of scrapie. Stockman also conducted anatomical investigations, and observed another important feature of scrapie, its neurodegenerative character, which had already been reported by two French researchers, Besnoit and Morel in 1898; their work showed that scrapie-affected brain was characterised by vacuoles, and certain histopathological changes in the medulla, spinal cord and peripheral nerves.[36] Stockman's observation was the first clinical examination of the neuropathological features of scrapie in Britain.

To sum up: the first scientific investigations on scrapie were closely associated with professionalisation of veterinary medicine in the late nineteenth and early twentieth century. The professionalisation of veterinary science played a role in consolidating scrapie research as a veterinary subject.[37] Scrapie was an important site for consolidating the identity of veterinary medicine as a research-based scientific enterprise, and for establishing what kinds of theories of disease causation (most notably the bacterial theory of infection) would command credibility among the scientific elite of the veterinary community. In short, research on scrapie played an important role in the process of veterinary institutionalisation.

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[35] **Ford, Brian** (1996) *BSE: the facts* (London: Corgi Books): 37; **McFadyean, John** (1918) *op. cit.* note 33

[36] **Besnoit, C. & Morel, C.** (1898) 'Notes sur les lesions nerveuses de la tremblante du mouton', *C.R. Soc. Biol. 5*: 536. Continental scientists tended to focus on the neurological features of scrapie rather than cutaneous features. Moreover, when naming the disease, more neurological features were articulated, for instance, *die Traberkrankheit* (the trotting disease), *das Drehen oder Traben* (Turning or trotting), *die Zitterkrankheit* (trembling disease) in Germany and *la maladie convulsive* (the convulsive disease), *la maladie folle* (the mad disease), *la tremblante* (trembling disease) in French. On the other hand, British scientists had a tendency to investigate the cutaneous features, which was why the name of disease also reflected this tendency; for instance, *rubbers, rickets, scratchie and scrapie.*

[37] For more on the issue of professionalisation of veterinary science, see **Pattison, Iain** (1984) *op. cit.* note 22; **Swade, Joanna** (1999) *Animals, Disease, and Human Society* (London: Routledge); **Fisher, John R.** (1993) 'Not quite a profession: the aspirations of veterinary surgeons in England in the mid nineteenth Century', *Historical Research 66*: 284-304; **Fisher, John R.** (1993) 'British physicians, medical science, and the cattle plague, 1865-66', *Bulletin of the history of medicine 67*: 615-669

4. Institutionalisation of scrapie research

Mention has been made of the national movement to professionalise veterinary medicine, but local demand to set up studies into the causes and nature of agricultural diseases was also a significant factor in the history of agricultural research. The participation of farmers and growers played an important role in establishing research institutes. For instance, one of the earliest agricultural research institutes was the National Fruit and Cider Institute at Long Ashton, founded by Robert Neville Granville under the sponsorship of the Bath and West and Southern Counties Society in 1903. The institute became the department of agriculture and horticulture at the University of Bristol.[38] Since that time, many other locally supported research institutes had also been established, and the Animal Diseases Research Association (ADRA) was one of them. The ADRA was established in 1920; it was set up by landowners and farmers, particularly sheep breeders in Scotland, to promote investigation into the diseases of livestock.[39] This initiative attracted support from the private sector and from the Development Fund through the Department of Agriculture for Scotland. This enabled the Association to establish permanently its Moredun Institute at Gilmerton, Edinburgh, in 1926.[40]

Another big step in the history of agricultural research was the establishment of the Agricultural Research Council (ARC) in 1931. The ARC was designed to complete the scientific organisation for the supervision of civil research.[41] The establishment of research institutes helped to promote the subject of scrapie research in Britain. In this context, scrapie became one of the primary research issues for veterinary scientists. One of the researchers in the Moredun Institute, S. H. Gaiger, published a detailed report of the clinical symptoms and epidemiological patterns of the disease in 1924.[42]

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[38] **Henderson, William** (1981) *op. cit.* note 24: 9

[39] **Dickinson, Alan G.** (1998) 'Transcription of oral hearings: day 31', *The BSE Inquiry* (11th June 1998, London: the BSE Inquiry): 12; **Angus, Kenneth** (1990) *A History of Animal Diseases Research Association* (Edinburgh: ADRA)

[40] **Henderson, William** (1981) *op. cit.* note 24: 12

[41] *Ibid.*, 21. For more detailed studies on the history of ARC, see **DeJager, Timothy** (1993) 'Pure science and practical interests: the origins of the Agricultural Research Council, 1930-1937', *Minerva 31*: 129-150

[42] **Gaiger, S.H.** (1924) 'Scrapie', *Journal of Comparative Pathology and Therapeutics 37*: 259-277

During the 1930s, scrapie was the main focus of the investigations at the Moredun Institute, following the demonstration of the presence of an inoculable factor in scrapie by two French scientists, Jean Cuille and Paul-Louis Chelle of Toulouse.[43] This was the first successful transmission experiment, and generally established the view that the disease was transmissible. This French success stimulated the British researchers to launch a variety of investigations into scrapie. By 1934, intensive microscopic studies of the disease had been carried out,[44] and by 1937, the disease was known to be caused by an infectious agent. There was convincing evidence of spread by contamination of the pasture.[45]

However, of greater significance, and with more explosive implications, was the accidental outcome of an experiment with louping-ill vaccine in 1935. A veterinarian, William Gordon, was working with other researchers on the development of a vaccine against louping-ill, which is another ovine disease that causes brain inflammation, lethargy, poor co-ordination and death within days. The vaccine Gordon's team developed consisted of homogenised brain, spinal cord and spleen tissue taken from sheep infected with louping-ill, diluted in saline solution and inactivated by adding a small amount of formaldehyde.[46] As William Gordon wrote, "this investigation had a more romantic turn and less fortunately a final dramatic twist which led almost to catastrophe."[47] In 1935, the vaccines were injected into sheep with the expectation that the inoculated animals would become immune to the louping-ill virus. It was successful. Within three years, however, the vaccinated flocks began to develop scrapie. According to Hugh Fraser, who was a researcher in

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[43] **Cuille, J. & Chelle, P.L.** (1936) 'La maladie dite tremblante du mouton est-elle inoculable?', *Comptes Rendus de Academie des Sciences* (Paris) 203: 1552-1554

[44] **ADRA** (1935) *Animal Diseases Research Association: Report 1934-1935* (Edinburgh: Moredun Institute): 17; **ADRA** (1936) *Animal Diseases Research Association: Report 1935-1936* (Edinburgh: Moredun Institute): 18; **Brownlee, A.** (1940) 'Histo-pathological studies of scrapie, an obscure disease of sheep', *The Veterinary Journal 96*: 254-264.

[45] **Angus, Kenneth** (1990) *op. cit.* note 39: 35-36; **ADRA** (1938) *Animal Diseases Research Association: Report 1937-1938* (Edinburgh: Moredun Institute): 14; **Greig, J. Russell** (1940) 'Observations on the transmission of the disease by mediate contact' *The Veterinary Journal 96*: 203-206

[46] **Rhodes, Richard** (1998) *Deadly Feasts: tracking the secrets of a terrifying new plague* (New York: Simon & Schuster): 59

[47] **Gordon, W. S.** (1946) 'Advances in veterinary research: louping-ill, tick-borne fever, and scrapie.' *The Veterinary Record 58* (47): 517

the Moredun Institute, the eventual toll was high - about seven per cent of the 18,000 immunised sheep.[48] Gordon immediately begun to suspect that the vaccine might be to blame. He later recollected:

> I visited most of the farms on which sheep had been vaccinated in 1935. It was at this point that the investigation reached its dramatic phase; I shall not forget the profound effect on my emotions when I visited these farms and was warmly welcomed because of the great benefits resulting from the application of louping-ill vaccine, whereas the chief purpose of my visit was to determine if scrapie was appearing in the inoculated sheep. The enquiry made the position clear. Scrapie was developing in the sheep vaccinated in 1935.[49]

As Gordon became concerned that scrapie had been transmitted with his vaccine, he set up an extensive experiment to confirm how this might have occurred. With funding from the ARC, he injected 788 sheep with scrapie-affected tissues in 1938. This experiment confirmed that the louping-ill vaccine incident was caused by the fact that the scrapie agent has a remarkable resistance to formalin. Gordon also recorded various incubation periods from about 9 months to 3 years, and observed the different susceptibility of different breeds of sheep to the disease.[50]

This accidental result of the experiment with louping-ill vaccine provided valuable field data to help researchers understand the mysterious disease of scrapie. It also allowed the characteristics of "experimental" scrapie to be studied in detail and to be compared to those of naturally occurring cases. What Gordon and his colleagues found was that the scrapie agent was too tough to be destroyed by conventional methods of inactivation such as formaldehyde. Iain Pattison, who was involved with this experiment as a pathologist, calls the experiment "the earliest flush of scrapie cases."[51] Following this accidental experiment, the Moredun Institute launched biochemical research on the disease.[52]

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[48] **Fraser, Hugh** (1996) 'Report for CJD litigation held in the High Court', (April-May, 1996: London) quoted from **Cooke, J.** (1998). *Cannibals, Cows, and the CJD Catastrophe* (London: Minerva): 31

[49] **Gordon, W. S.** (1946) *op. cit.* note *47*: 517

[50] *Ibid.*

[51] **Pattison, I. H.** (1992) 'A sideways look at the scrapie saga: 1732-1991', S. B. Prusiner, J. Collinge, J. Powell and B. Anderton (eds), *Prion Diseases of Humans and Animals* (New York: Ellis Horwood): 16

[52] **Angus, Kenneth** (1990) *op. cit.* note 39: 35-36

During the war, most of veterinary research was curtailed, and work in several areas of scrapie research had ceased.[53] Only David R. Wilson at the Moredun was able to continue his project on scrapie after 1939. Between 1939 and 1953, Wilson conducted a variety of experiments into the means of scrapie infection.[54] What he found were some quite extraordinary features, from the conventional point of view on the properties of viruses and bacteria.

Though he failed to isolate the infectious agent, his remarkable achievement provided a benchmark for other scientists. Firstly, he reported that the agent was filterable, which meant that it must be very small – smaller than bacteria.[55] Secondly, the agent was highly resistant to heat, formalin, phenol and chloroform.[56] Third, the scrapie agent remained viable in the desiccated state at 0° to 4°C for long periods; the agent survived in dried brain tissue for a period of over two years.[57] Fourth, exposing infected brain samples to a considerable dose of ultraviolet light failed to inactivate the scrapie infection. Lastly, the scrapie agent also survived steam treatment in an autoclave, which usually kills most bacteria and viruses. These results implied that normal disinfectants had little effect on the scrapie agent.[58] The scrapie agent was so unusual that Wilson hesitated to publish his results. Indeed, his main experimental data have never been published. Instead, the data were circulated among small numbers of researchers who were also concentrating on scrapie research.[59] Moreover, Wilson himself was not only hesitant about publishing his data, but was also under enormous pressure from the ARC to come up with a vaccine against scrapie. He failed in this aim, and his enormous contributions have since been forgotten and

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[53] *Ibid.*, 45

[54] **ADRA** (1942) *Animal Diseases Research Association: Report 1941-1942* (Edinburgh: Moredun Institute): 14

[55] **Wilson, D. R., R. D. Anderson, et al.** (1950) 'Studies in scrapie', *Journal of Comparative Pathology* ***60***: 267

[56] **Pattison, I. H.** (1992) *op. cit.* note 51: 16

[57] **Wilson, D. R., R. D. Anderson, et al.** (1950) *op. cit.* note 55:278

[58] **Ford, Brian** (1996) *op. cit.* note 35: 39-40

[59] Fortunately, Wilson's experimental achievements and his data were recorded by his colleagues, see **Stamp, J. T., J.G. Brotherston, et al.** (1959) 'Further studies on scrapie', *Journal of Comparative Pathology* *69*: 268-280

ignored.[60] According to Alan Dickinson, who was a colleague at the Moredun during the 1950s:

> D.R. Wilson did enormously significant founding work and he had a nervous breakdown. He had a nervous breakdown because the Agricultural Research Council were extremely critical that he hadn't produced a vaccine yet, and he had been working on it for about two years. [...] It was a bandwagon: 'make a vaccine if it is an infection, make a vaccine.' [...] The bureaucrats did not understand why someone should be wanting to boil things.[61]

5. Intensive research projects in Edinburgh and Compton

In the 1950s, the scrapie epidemic was worsening on a global scale; in Canada there was the first scrapie case in 1940;[62] scrapie appeared in Australia in the summer of 1951; the United States Department of Agriculture (USDA) issued a declaration of a state of emergency with reference to scrapie in sheep in 1952;[63] and the first outbreak of scrapie in New Zealand occurred in 1952.[64] Epidemiological investigations revealed that every outbreak in those regions was closely related to imported flocks from Britain. These countries therefore placed an embargo on British sheep, and there was huge pressure to develop research on scrapie in order to eradicate the disease.

Although there was an outbreak of scrapie in America, there were no laboratories in the US set up to study scrapie. The British had the laboratories and the "USDA [United States Department of Agriculture] found money left over from the Second World War - a programme funded to insure that food procured for US troops abroad was safe - to support the work."[65] The USDA grant was allocated to the Institute for

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[60] *Ibid.*, 40

[61] **Dickinson, Alan G.** (1999) Interview with author (Dunbar: 15 September 1999)

[62] **Plummer, P. J. G.** (1946) 'Scrapie - a disease of sheep', *Canadian Journal of Comparative Medicine* ***10***: 49-54

[63] **Anonymous** (1952) 'Scrapie found in California sheep', *Journal of the American Veterinary Medical Association* ***121*** (December 1952): 455; **Wagner, A. R., H. E. Goldstein, et al.** (1954) 'Scrapie-a study in Ohio' *Journal of the American Veterinary Medical Association* ***124*** (February 1954): 136-140

[64] **Brash, A. G.** (1952) 'First outbreak of scrapie reported in New Zealand', *New Zealand Journal of Agriculture* ***85***: 305-306

[65] **Rhodes, Richard** (1998) *op. cit.* note 46: 60

Research on Animal Diseases (hereafter IRAD) at Compton and the Moredun Institute. The ARC had a farm research centre at Compton, Berkshire, referred to as the "Field Station" until the name was changed in 1963 to IRAD. The field station was the first ARC research institute, and was designed to research mainly on cattle diseases.[66] The USDA grant initiated the first large-scale involvement of IRAD in scrapie research. Before the involvement of IRAD, the Moredun Institute was the only place conducting large-scale scrapie experiments. According to the Director of the Moredun Institute, John Stamp, the aims were two-fold: "to determine whether a virus is in fact present all the known methods of microbiological research are being followed, while to investigate the possible latency factor a number of different breeds of sheep are being tested, the former work at Moredun, the latter at the Agricultural Research Council Unit at Compton".[67]

When William Gordon moved down from the Moredun to take over as director at Compton in 1942, he wanted to set up a large-scale scrapie experiment in the vast dairy farms at Compton. With USDA funds, Gordon was able to launch this programme. In 1954, William Gordon assembled between 30 and 57 sheep of each of 24 different breeds - 1,027 in all - in order to investigate their differential susceptibility to scrapie. This experiment became known as the "24-breed experiment". The result revealed an incidence of scrapie ranging from 78% in Herdwicks to nil in Dorset Downs.[68] This mammoth project continued until 1973, even after Gordon's death.[69] Moreover, the ARC agreed that Wilson's research project in the 1940s should be extended, and this task was allocated to the IRAD at Compton. However, before 1957 IRAD did not possess extensive facilities for microbiological and biochemical research. When the ARC commissioned the institute to launch an extended programme of microbiological work, Gordon set up four departments for scrapie work: biochemistry (under Gordon Hunter), functional

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[66] **Henderson, William** (1981) *op. cit.* note 24: 29-31

[67] **ADRA** (1956) *Animal Diseases Research Association: Report 1955-1956* (Edinburgh: Moredun Institute): 24

[68] **Gordon, William S.** (1964) 'Review of work on scrapie at Compton, England, 1952-1964', Report *of Scrapie Seminar* (Washington: USDA): 19-40

[69] **Pattison, I. H.** (1988) 'Fifty years with scrapie: a personal reminiscence', *Veterinary Record* 123(26-27): 662

pathology (Richard Chandler), pathology (Pattison), and microbiology (David Haig). Each department launched specific projects on scrapie.[70]

On the other hand, in Edinburgh under the leadership of Stamp, the Moredun team launched another experimental project on scrapie, involving chemical, microbiological and microscopic studies. As Stamp mentioned, the Moredun team focused on the microbiological and chemical work, which was carried out by the existing research teams in the institute.[71] Furthermore, Stamp was also interested in the genetic features of the disease, hence he planned to set up new project on genetic research. One problem was, however, that the institute did not have good animal facilities for genetic research. Traditionally, the primary project of the institute was microbiological and virological research on various sheep diseases. Hence, Stamp suggested setting up a collaborative team with the Animal Breeding Research Organisation (hereafter, ABRO). ABRO was a part of the Institute for Animal Genetics that was established by the Development Commission in 1921. Soon after the establishment of the ARC, the institute came under ARC funding and control. In 1945, the Council and the Agricultural Improvement Council decided that it should be concerned with fundamental genetic principles based on the results of a series of long-term observations. In 1951, the Council decided to split the animal breeding part and genetics part. Thereafter, the ABRO became an independent institute responsible for animal breeding work.[72] The institute was devised with six field stations, and maintained approximately 900 cattle, 7,000 sheep, and 2,000 pigs. The staff of ABRO were collectively engaged in a number of considerable farming enterprises at the time.[73] Consequently, Stamp considered ABRO a promising place to launch the genetic research on scrapie.

In 1955, Stamp and H. P. Donald (who was a director of ABRO) agreed that they should organise a collaborative research team to investigate the genetic features of

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[70] **Gordon, William S.** (1964) *op. cit.* note 68

[71] **ADRA** (1956) *op. cit.* note 67: 24

[72] **Henderson, William** (1981) *op. cit.* note 24: 43-44

[73] **ABRO** (1963) *Animal Breeding Research Organisation – Report, 1963* (Edinburgh: Animal Breeding Research Organisation): 7-8

scrapie. This project was also supported by a grant of £ 54,000 from the USDA.[74] John Stamp stated the aim of project in the Moredun Institute's annual report in 1956:

> Although the evidence of the transmissibility of scrapie is of first importance, the doubt as to the living nature of the agent, linked with the considerable field evidence of a breeding factor, make it essential to carry out a controlled breeding experiment to determine whether in fact any genetic factors enter into the causation of the disease.[75]

The Moredun-ABRO joint project unit[76] was led by a geneticist, Alan G. Dickinson, a veterinarian Gilbert Young and a pathologist, Ian Zlotnik. Later, instead of Young and Zlotnik, a Cambridge-graduate neuropathologist, Hugh Fraser, and biologist George Outram became involved in the project.

Not surprisingly, the large scale projects in Edinburgh and Compton included some overlapped subjects: each project included work on the microbiology, biochemistry, pathology and genetics of scrapie (see the table 2).

Subject	IRAD	Moredun-ABRO
Director	William Gordon	John T. Stamp
Microbiology/Virology	David Haig	Derek Mould
Biochemistry	Gordon Hunter	John Brotherson
Pathology	Iain Pattison	Ian Zlotnik
Genetics	William Gordon	Alan G. Dickinson

Table 2: Overlapped subjects and researchers in IRAD and Moredun-ABRO

As a result, the ARC decided to set up a working party to oversee the research in Edinburgh and Compton. The Technical Committee on Scrapie Research (also known as the Scrapie Working Party) was set up in 1961. One of the members of the head office of the Council, Scarisbrick, was appointed to the chairmanship.

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[74] **Angus, Kenneth** (1990) *op. cit.* note 39: 56

[75] **ADRA** (1956) *Animal Diseases Research Association, Report 1955-1956* (Edinburgh: Moredun Institute): 26

[76] Sometimes this team was called the ADRA (Animal Diseases Research Association)-ABRO (Animal Breeding Research Organisation) joint project unit

The working party also included many of those involved in the overlapping research: from the Compton side, Gordon, Haig, Hunter and Pattison became delegates; the Moredun side was represented by Stamp, Zlotnik, Brotherson, and Mould. Between 1961 and 1969, the working party functioned as a regulatory body to co-ordinate the whole project. The relationship between the two teams in Edinburgh and Compton was maintained through the scrapie working party.

During the 1960s, the newly launched large-scale programmes in the UK produced valuable research outcomes and speculations. As we shall discuss in following chapter, the two research teams suggested quite opposite and conflicting ideas about the nature of the disease. Although the research programmes discovered unusual properties of scrapie, which could help to understand the mechanism of the disease, the relations between the two centres would quickly became strained, and eventually led to open controversy and rivalry during the 1960s and 1970s.

6. Summary

In this chapter, I have briefly reviewed the history of scrapie research between 1750 and 1960. Arguably, scrapie has a long history in Britain, and has caused serious economic losses. Since scrapie was identified as an individual sheep disease by pioneering veterinary researchers in the 1910s, there has been persistent pressure from farmers and sheep breeders to pursue scientific investigations. Consequently, privately funded research institutes were established, such as the Moredun Institute, and the government also supported research on scrapie by founding the Agricultural Research Council (ARC) in 1931. With a large-scale epidemic in the 1930s, scrapie became recognised amongst veterinary scientists as one of the top priority research subjects.

During the 1940s and 1950s, the Moredun Institute conducted a variety of research projects on scrapie, and brought to light some puzzling features of the disease. David Wilson's work and the louping-ill vaccine incident provided valuable experimental data for subsequent researchers, and valuable primary knowledge for the understanding of the disease. Furthermore, in the 1950s, the ARC decided to set up

new research programmes on scrapie in Edinburgh and Compton. These projects would produce valuable results and controversial hypotheses.

In sum, the whole process of disease recognition was closely associated with the institutionalisation of research on the disease. In particular, the institutional settings of veterinary and agricultural science played an important role in developing the research on scrapie. In the early days, a scrapie-like disease was recognised in terms of local knowledge. Knowledge of the disease was largely embodied in the crafts and practices of local farmers and shepherds. However, with the professionalisation of veterinary medicine, scrapie became recognised as an independent disease in sheep. In the first half of the twentieth century, scrapie became one of the main veterinary subjects. The whole process of disease recognition was, in fact, closely associated with development and institutionalisation of veterinary medicine.

Chapter 3 - Genetic research into scrapie at the Moredun Institute, Edinburgh, 1964-1979

1. Introduction

In the 1960s, scrapie was regarded as a mysterious and arcane subject in veterinary science, due to its extraordinary characteristics, such as long incubation period, absence of immune reactions, and strong resistance of absent to physico-chemical treatments. In 1961, there was an important experimental breakthrough; a researcher at the Institute for Research on Animal Diseases (IRAD), Richard Chandler, succeeded in infecting laboratory mice with the disease.[1] This successful transmission enabled scientists to conduct various experiments on the disease in the laboratory. One particular group to benefit from this success was geneticists. For genetics, laboratory animals have long been a crucial element the investigation of gene action. Since the early twentieth century, when full-scale scientific studies on scrapie began, the biggest obstacle was the impossibility of carrying out laboratory studies. Due to the lack of appropriate laboratory animals, geneticists had to conduct experiments in the field. Field experiments with sheep took a long time to produce results. For this reason, the transmission of scrapie into laboratory animals was a significant breakthrough.[2] At long last, geneticists could now launch laboratory experiments into the nature of scrapie.

One of the genetic research teams was based on collaboration between scientists at the Moredun Institute and the Animal Breeding Research Organisation (ABRO) in Edinburgh, a collaborative team led by a geneticist, Alan G. Dickinson. For nearly 20 years, Dickinson examined the genetic features of the disease, and produced an

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[1] **Chandler, R. L.** (1961) 'Encephalopathy in mice produced by inoculation with scrapie brain material', *The Lancet* **1**: 1378-1379

[2] Around the late 1950s, at least three teams of researchers carried out transmission experiments in both Compton and Edinburgh: led by Richard Chandler (IRAD at Compton), Ian Zlotnik (Moredun at Edinburgh), and Alan Dickinson (Animal Breeding Research Organisation at Edinburgh). The race for transmission ended with Chandler's success.

explanatory model of the nature of scrapie in the 1970s. He suggested that scrapie infection occurs by means of a very small virus-like agent, but the replication of the infection is dependent on the genetic properties of the host. During the 1970s, his explanatory model achieved high levels of credibility within the research community.

The aim of this chapter is to examine how Dickinson and his group built up their experimental programme. In particular, I will outline the complicated series of genetic-pathological experiments that Dickinson designed and carried out. The main aim is to explain how Dickinson and his group at Edinburgh produced a genetical and pathological explanation of the strain variation of the scrapie agent. Furthermore, it will be shown how the Edinburgh researchers coped with uncertainties in the field, and how the uncertainties were translated into something approaching certainty through experimental results. Finally, this chapter also describes how Dickinson used these results to formulate a hypothesis on the nature of scrapie.

2. Early Works of Dickinson: Genetic or Contagious Disease?

By the mid-fifties, some scientists were beginning to look into the genetic dimension of scrapie. The genetic aspect of scrapie was a contentious issue in the scientific community. This approach, in fact, was associated with public suspicion of the disease: farmers had long held a suspicion that the disease might be inherited rather than infectious. As seen in the previous chapter, since a scrapie-like disease was reported in the eighteenth century, many writers speculated that it might be caused by genetic problems, though their number declined in the wake of the mid-nineteenth century interest in infectious disease. However, during the early years of the twentieth century, in view of the failure to isolate a viral agent, and of the anomalous properties of the hypothetical infectious agent, some scientists were now reconsidering the possibility that scrapie was indeed caused by a genetic defect.

[**Fraser, Hugh** (1999) Interview with author (Edinburgh: 30 June 1999); **Dickinson, Alan G.** (1999) Interview with author (Dunbar: 15 September 1999)]

This view was zealously asserted by an Oxford-based scientist, Herbert B. Parry. In particular, Parry stated that there was no evidence to suggest the spread of the disease from affected animals to others of the same generation by contact, coitus or contaminated environment.[3] Parry claimed that scrapie was a genetic disease due to a single autosomal recessive gene.[4] His argument was supported by many sheep breeders and some sceptics who did not believe in the viral origin of scrapie.

In addition, researchers in Compton conducted a series of field experiments on sheep from the early 1950s. This indicated that host susceptibility to scrapie is genetically determined. In other words, different genetic strains of sheep exhibit differential susceptibility to the disease.[5] Meanwhile, other workers at Compton, Pattison and Mills, suggested that different strains of the disease itself existed, suggesting that the virulence and clinical expression of the disease might vary specifically, they identified two different strains: drowsy and scratching.[6]

In this context, other veterinary researchers saw a need at this juncture to explore the genetic dimensions of scrapie. In 1955, a collaborative project in Edinburgh between the Moredun Institute and the Animal Breeding Research Organisation (hereafter, ABRO) was established to explore the possible genetic dimension of the disease. This project was led by Alan G. Dickinson, a geneticist trained at the University of Birmingham, who joined the staff of ABRO. As seen in the previous chapter, the Moredun institute had a long tradition of scrapie research since the 1920s. In 1955, the director, Russell Greig, retired from the directorship, and the veterinary researcher, John T. Stamp, took over the position, stating that the priority of research in the institute was to be scrapie research.[7] The Moredun-ABRO researchers launched animal breeding experiments to investigate whether scrapie

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[3] **Parry, H. B.** (1960) 'Scrapie: a transmissible hereditary disease of sheep', *Nature* ***185*** (4711): 441-443

[4] *Ibid.*, 442

[5] For example, William Gordon's twenty-four breed experiment was designed to investigate genetic susceptibility to scrapie with sheep in the field. **Gordon, William S.** (1964) 'Review of work on scrapie at Compton, England, 1952-1964', *Report of Scrapie Seminar* (Washington: USDA): 19-40

[6] **Pattison, I. H. and G. C. Millson** (1961) 'Scrapie produced experimentally in goats with special reference to the clinical syndrome', *Journal of Comparative Pathology* ***71***: 101-108

[7] **Stamp, J. T.** (1957) 'Address by Director of the Moredun Institute', *Animal Diseases Research Association: Annual Report and Accounts: 1956-1957* (Edinburgh: Moredun Institute): 18-25

could indeed be explained as a genetically inherited condition, or whether it was better understood as an infectious disease.[8]

Dickinson and Stamp obtained some suggestive experimental results in opposition to the recessive gene theory. First, according to Stamp, the Moredun Institute had evidence of infection by contact in sheep.[9] Since 1952, the Moredun and ABRO had maintained a brain pool affected by scrapie, which was called SSBP/1 (*S*crapie *S*heep *B*rain *P*ool). The SSBP/1 scrapie source had played a large part in scrapie research. The source was originated in 1945 by David Wilson from three natural cases, and had been passaged largely through Cheviot sheep.[10] In order to investigate the infectivity of scrapie, researchers in the Moredun inoculated material obtained from SSBP/1 into goats and sheep. Then, if the normal sheep were mixed with the experimentally scrapie-affected sheep, and had prolonged contact with a day-old infected sheep, contact transmission of scrapie from sheep to goats occurred. Second, other researchers at Moredun, MacKay and Smith,[11]also reported cases of possible contact infection in goats. A scrapie-free goat was put with scrapie-inoculated goats. A year later, the scrapie-free goat manifested symptoms of scrapie (scratching, lack of co-ordination). MacKay and Smith agreed that this occurrence of scrapie without inoculation was a result either of the natural infection or of contact infection of scrapie.[12] This observation was contradictory to Parry's theory of a recessive gene. Finally, in the meantime, Dickinson and Stamp investigated the possibility of simple inheritance of scrapie in sheep. If a lethal recessive gene was solely responsible for causing the disease, as Parry suggested, then a recognised familial pattern should occur. If scrapie was due to a single recessive gene, then the incidence of scrapie should be the same in the offspring of affected rams and

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[8] **Stamp, J. T.** (1962) *Annual Report of Animal Diseases Research Association 1960-1961* (Edinburgh: Moredun Institute): 23

[9] **Stamp, J. T.** (1962) 'Scrapie: a transmissible disease of sheep', *The Veterinary Record* **74** (12): 357-362

[10] **Dickinson, A.G., Smith, W.** (1964) 'Adaptation of the SSBP/1 scrapie agent from sheep to mice', *Report of Scrapie Seminar, ARS 91-53* (Washington: Agricultural Research Service, USDA): 251-252

[11] J.M.K MacKay is a microbiologist, and B.S.W. Smith is a biochemist in the Moredun Institute.

[12] **MacKay, J. M. K., W. Smith** (1961) 'A case of scrapie in an uninoculated goat-a natural occurrence or a contact infection?', *The Veterinary Record* 73(16): 394-396

affected ewes. However, the experiment indicated that the offspring of affected ewes had a high probability of developing scrapie, while the offspring of affected rams had a much lower probability. This was inconsistent with the hypothesis that scrapie was caused by a single autosomal recessive gene.[13]

Meanwhile, Dickinson and his colleagues at the Moredun-ABRO joint unit were producing further evidence to indicate that scrapie was indeed both infectious and contagious. Once Richard Chandler has shown that scrapie can be transmitted into laboratory mice, Dickinson and Stamp built on experimental work with laboratory mice. They investigated in more detail the phenomenon of contact transmission from 1961.[14] The main aim of this experiment was to demonstrate infection between mice by contact. Scrapie-free were mice mixed with experimentally scrapie-infected mice in the same cage. Consequently, some of the scrapie-free mice became infected by scrapie, and developed the distinctive pathological features of the disease (spongiform change in certain regions of brain). This suggested that, in this case at least, scrapie was not a genetical disease, but a contagious one.

As a result, the Edinburgh researchers now became increasingly firm in their conviction that scrapie is an infectious disease.[15] It remained under just what sort of infectious agent might be responsible, however. This was due to constant failure of isolating the agent, and continued awareness of the anomalous properties of the putative agent. Hence, scientists were continually reluctant to state that the agent of scrapie was a virus. This reluctance in the scientific community can be seen in the case of definition of the disease. At the time, many defined the disease as a 'slow infectious virus', an idea suggested by an Icelandic veterinary researcher,

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[13] **Stamp, John T.** (1962) *op. cit.* note *8*: 24; **Dickinson, A.G., J.T. Stamp** (1962) unpublished work

[14] **Dickinson, A. G., J.M.K. MacKay, I. Zlotnik** (1964) 'Transmission by contact of scrapie in mice', *Journal of Comparative Pathology* ***74***: 350-254

[15] From their early works on scrapie, for instance, **Greig** (1950) and **Wilson *et. al.*** (1950) to papers around 1960, most Moredun researchers held that scrapie was an infectious and transmissible disease in sheep and goats. See **Greig, J. R.** (1950) 'Scrapie in sheep', *Journal of Comparative Pathology* ***60***: 263-266; **Wilson, D. R., R. D. Anderson, W. Smith** (1950) 'Studies in scrapie', *Journal of Comparative Pathology* ***60***: 267-282; **Zlotnik, I., J.C. Rennie** (1962) 'The pathology of the brain of mice inoculated with tissues from scrapie sheep', *Journal of Comparative Pathology* 72: 360-365; **Stamp, J. T., J.G. Brotherston, I. Zlotnik, J.M.K. Mackay,**

Sigurdsson. Sigurdsson suggested that some diseases like Rida (scrapie in Iceland), Visna and Maedi showed symptoms which developed very slowly.[16] Although his concept could not explain the whole anomalous mechanism of scrapie, the scientific community was attracted to this novel concept, and it gained international support.

3. Investigating the involvement of host genes: developing a standardised experimental system

As seen, Dickinson carried out these early and relatively simple experiments to distinguish whether scrapie was an infectious or genetic disease. He had established, at least to his own satisfaction, that scrapie is an infectious disease. Around 1961, Dickinson and his colleagues pursued a more complex and long-term experimental project to investigate some rather different aspects of the disease. At the time, other scientists, especially at Compton, were endeavouring to study biochemical aspects of the nature of the agent. However, Dickinson had a different research aim from the others: he preferred to use pathological and genetic techniques to investigate the ways in which the disease developed and progressed in infected organisms.

Dickinson was interested in the fact that the incubation period of scrapie could vary considerably from one individual of a given species to another. As a geneticist, he was particularly interested in the possibility that this might be due at least in part to variations in the genetic constitutions of the infected animals. Consequently, Dickinson developed a series of experimental projects that were intended to explore the possibility of genetic involvement.

The genetic investigation at the Moredun-ABRO unit was greatly aided by the fact that scrapie could now be transmitted to laboratory mice, which had been carried out serially and successfully by researchers in Compton then Edinburgh in

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W. Smith (1959) 'Further studies on scrapie', *Journal of Comparative Pathology* **69**: 268-280; **Stamp, J. T.** (1962) *op. cit.* note 9

[16] **Sigurdsson, B** (1954) 'Rida: a chronic encephalitis of sheep', *The British Veterinary Journal* ***110***: *341*-354

1961.[17] The successful transmission to laboratory animals was far more satisfactory than working with the natural host of scrapie, i.e., sheep and goats. There are a number of reasons why working with laboratory animals was more effective: first, the progress of scrapie in sheep and goats is very slow, so experiments based on measuring incubation periods would take a long time, whereas its progress in mice is much quicker, greatly speeding up the experimental procedure. Second, geneticists and other biomedical researchers had been maintaining and breeding populations of mice in a variety of laboratories since the early twentieth century.[18] Some of these had become quite inbred, and hence relatively genetically homogeneous; indeed, scientists were increasingly exploiting this homogeneity for standardising various experimental procedures. Consequently, geneticists already knew a considerable amount about the genetic constitution and variability of some of these various mouse stocks, and certainly more than they knew about the genetics of even relatively pure bred farm animals such as the Moredun Institute's own flock of Cheviot sheep. And finally, Dickinson and his colleagues plainly envisaged that any investigation of the influence of host genetics on the development of scrapie would involve the standard techniques of genetic investigation, i.e. controlled breeding experiments. However, the relatively long life cycle of sheep and goats was a major hindrance to pursuing such methods. In his directorial address in 1957, Stamp remarked on the difficulties of conducting genetic research with sheep and goats:

> Although all this work [pathological and microbiological researches] suggests that the cause of scrapie is a virus, we are still in conjunction with the Animal Breeding Research Organisation, carrying on with our extensive genetical investigations for, as many of you know, it is becoming increasingly difficult to differentiate a virus from a

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[17] Around the early 1960s, researchers both from Edinburgh and Compton reported that they succeed in transmitting the agent into various laboratory animals: mice [**Chandler, R. L.** (1961) *op. cit.* note 1], hamsters [**Zlotnik, I** (1963) 'Experimental transmission of scrapie to golden hamsters', *Lancet, ii*: 1072], and rats [**Chandler, R.L., & Fischer, J.** (1963) 'Experimental transmission of scrapie to rats', *Lancet, ii*: 1165].

[18] **Rader, Karen A.** (1997) 'The origin of mouse genetics', *Mammalian Genetics* 8: 464-466; **Rader, Karen A.** (1998) '"The mouse people": murine genetics work at the Bussey Institution, 1909-1936', *Journal of the History of Biology* 31: 327-354; **Rader, Karen A.** (1999) 'Of mice, medicine and genetics: C.C. Little's creation of inbred laboratory mice, 1909-1918', *Studies in History and Philosophy of Biology and Biomedical Science* 30 (3): 319-343

gene. Such genetical studies in sheep do however take many years and I, as well as you, must be patient.[19]

While examining the effect of the genetic constitution of the mouse host on the incubation time of scrapie, Dickinson was well aware that other factors might also influence incubation time. For instance, it was well known that in many infectious diseases the speed with which the disease developed was influenced by the dose of infectious agent to which an organism was exposed.

If he was going to look at the influence of host genetics on the incubation period of scrapie, then he had to ensure that any such peripheral effects were eliminated. In effect, variation in the incubation period resulting from differences in the genetic make-up of his experimental mice was the signal he wished to observe, while variation in the incubation period resulting from variation in the dose of infectious material would be noise in his experimental set up. Hence, in order to minimise such noise, Dickinson took considerable pains to standardise the doses of infectious material he injected into his mice.

Efficient means of measuring infectivity were made possible by the successful transmission of scrapie into the laboratory mouse.[20] The relatively short incubation time made it possible for researchers to assay scrapie infectivity. In the early 1960s, a group of researchers developed a method of titrating infectivity.[21] Groups of 6-10 animals were inoculated with serial 10-fold dilution of the inoculum being tested. In other words, a series of dilutions containing 0.1 per cent, 0.01 per cent and so on, was made, and injected into animals. Then, every month the number of animals at each dilution that developed the disease was recorded until all animals had died.[22] At very high dilutions, it may be that no animals succumbed to disease. At very low dilutions (i.e. higher concentrations) they might all do so. The dilution at which 50 per cent of the animals acquire the disease defined the unit of infective dose (ID_{50}).

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[19] **Stamp, J. T.** (1958) 'Address by Director of the Moredun Institute', *Animal Diseases Research Association: Annual Report and Accounts: 1957-1958* (Edinburgh: Moredun Institute): 17

[20] **Chandler, Richard L.** (1961) *op. cit.* note *1*

[21] **Mould, D. L., Dawson, A. M., Smith, W.** (1967) 'Determination of the dosage-response curve of mice inoculated with scrapie', *Journal of Comparative Pathology 77*(4): 387-391

[22] **Kimberlin, R. H.** (1976) *Scrapie in the Mouse: a Model Slow Disease.* (Durham: Meadowfield): 8

By definition, 1 ID_{50} unit is the dose necessary to give a 50 per cent probability of causing disease in an animal. For example, if a 0.001 per cent dilution of infective material results in the death of 50 per cent of animals, the original material before dilution is known to contain 1,000 ID_{50} units per gram.[23]

This method was called, "end-point titration", and it became a standard method for assaying scrapie infectivity. The method was not without its drawbacks. As Gordon Hunter, a leading biochemist in IRAD, claimed, "the biological titration of the scrapie agent in mice is a tedious affair, and simpler methods of assay have been continuously sought".[24] Nevertheless, the accuracy of the method was regarded as being beyond doubt. Moreover, the assaying titration was a necessary step for conducting quantitative studies on scrapie. This new titration method is still recognised as the standard and most accurate method by most researchers.

Dickinson's awareness of the involvement of host genetics was heightened by his own efforts to refine this titration method. Dickinson claimed that "the optimum type of animal for this purpose is one with minimum response time, minimum genetic variability and maximum phenotypic stability to extraneous environmental variables."[25] Dickinson and his colleagues observed, when injecting scrapie into the mice stock of Moredun mice, that there was a certain spread of variation in the incubation period. They hypothesised that this was due to the genetic variation in their mouse stock. Hence, they thought that if the variation of incubation could be narrowed, then they could achieve an optimum type of laboratory mice for bioassay.

For this purpose, Dickinson selected nine different lines of mouse stock, of which five were different standard inbred mice (SM, BSVS, RIII, LG, and C57BL)[26] and four were semi-inbred mice from Moredun. When equal doses of scrapie was inoculated into each line of stock, they found that various ranges of incubation periods were manifested. In the case of standard inbred mice, they displayed close similarities in

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[23] **The BSE Inquiry** (2001) *The BSE Inquiry: Report Vol. 2* (London: The BSE Inquiry): 18

[24] **Hunter, G. D.** (1974) 'Scrapie', *Progress in Medical Virology* ***18***: 294

[25] **Dickinson, A.G., Mackay, J.M.C.** (1964) 'Genetical control of the incubation period in mice of the neurological disease, scrapie', *Heredity 19*: 280

[26] For short history of these different mouse strains and its various characters, see the full database of Jackson laboratory. [**Jackson Laboratory** (1998) "Inbred Strain"

response to scrapie: the incubation time shown was from 20.8 to 22.7 weeks. In contrast, the semi-inbred mice showed significant and marked differences from each other. This variation was taken to be evidence of residual heterozygosity.[27] In this experiment, Dickinson and MacKay concluded that "there was on average a wide range of incubation periods between strains extending from 20 to 40 weeks, and this aspect of the disease is evidently under a high degree of genetic control."[28] From this experiment, Dickinson was able to separate out a number of relatively inbred and genetically homogeneous mouse lines, each of which showed a distinct and relatively narrowly distributed spread of incubation period when inoculated with standard doses of scrapie agent.

In the experiments just described, the variation in incubation time due to variations in host genetics was in effect the signal they sought to isolate from the background noise produced by other sources of variation. As a result of the experiments, Dickinson produced a number of genetic mouse lines in each of which the influence of host genetics on incubation time does not vary from one individual to another. This type of mice could in effect be regarded as a standardised culture medium in which the scrapie agent could be cultivated. By cultivating scrapie in such standard laboratory mice, they were now in a position to look for other sources of variation in the incubation period. As a result of this further standardisation of their experimental system, Dickinson and his colleagues were now able to go to perform yet more very fruitful experiments with scrapie.

4. Demonstrating strain variation in scrapie

Around 1961, Dickinson launched a long-term experimental project to detect genetic variations in the disease itself. The basic question at the centre of his project was distinct from other investigations on scrapie. There are several reasons why Dickinson focused on the genetic variations of scrapie: first, among other things,

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www.informatics.jax.org; **Rader, Karen A.** (1997) *op. cit.* note 18; **Rader, Karen A.** (1998) *op. cit.* note 18; **Rader, Karen A.** (1999) *op. cit.* note 18]

[27] **Dickinson, A.G., Mackay, J.M.C.** (1964) *op. cit.* note 25: 287-288

[28] *Ibid.*, 288

Dickinson had been struck by a phenomenon already demonstrated by other researchers, who had reported clinically of different strains of the disease. According to Pattison and Millson[29], when sheep scrapie was transmitted to goats, the infected animals two distinct sets of symptoms: one called 'drowsy', and the other 'scratching'. The drowsy type had a shorter incubation period than the scratching one. The two types of scrapie also differed in other ways. Notably, while Chandler succeeded in transmitting the drowsy type into laboratory mice, attempts to transmit the scratching type were unsuccessful.[30]

As a geneticist, Dickinson was interested in how differences between organisms were determined and inherited. Consequently, he regarded the isolation of two distinct strains as a fundamentally interesting feature of scrapie. He, therefore, set out to see if he could elucidate this phenomenon further in the laboratory. Specifically, Dickinson and his colleagues set out to see if they could isolate different strains of scrapie in his laboratory mice. At the time, most scientists were using physico-chemical methods to attempt to identify the agent of scrapie. He later explains his own interests to the BSE inquiry in 1998:

> [W]hen most people were saying: "we want to know what the nature of this (scrapie) agent is," and I starting as a geneticist, said: "I think a more fundamental question is: 'what is the nature of agent variation?'" It is that distinction which still rumbles as confusion through many documents, and has protruded into some of the evidence given. It is a very important distinction. If you think about it, there are those who claim, I think prematurely, that they know what the nature of the agent is in chemical terms. The outstanding question is very much: "what are strain differences?" "What is the nature of agent variation?"[31]

This research task was greatly facilitated by the high degree of standardisation that he had already developed in his system of cultivating scrapie experimentally. Having standardised both the dosage of infectious material and the media (i.e. the inbred mouse strains) in which that material was cultivated, Dickinson was now in position to identify any variations in the pathological manifestation of the disease

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[29] **Pattison, I. H., G. C. Millson** (1961) 'Experimental transmission of scrapie to goats and sheep by the oral route', *Journal of Comparative Pathology* **71**: 171-176

[30] **Chandler, Richard L.** (1961) *op. cit.* note *1*; **Chandler, Richard L.** (1962) 'Encephalopathy in mice', *Lancet 1*: 107-108

that might result from variations in the infectious agent. Consequently, his team at Edinburgh conducted an extensive series of inoculation experiments, using scrapie material from a variety of sources to see if such variation did indeed occur.

Dickinson's investigations into strain variation in scrapie were greatly facilitated by the work of one of his colleagues at Moredun, Ian Zlotnik. Richard Chandler had only succeeded in transmitting a single type of scrapie – the drowsy type in goats – into laboratory mice. But in 1963, Zlotnik managed to transfer scrapie from Suffolk sheep into mice. This proved to be quite different from Chandler's strain. The new strain – named ME7 (*M*ouse *E*ncephalopathy-7)[32] – had a shorter incubation period, and produced white matter vacuolation in the brain whereas Chandler's strain produced grey matter vacuolation.

Following on this success, Dickinson and his colleagues developed a standardised protocol for identifying and describing any variations in the patterns of neurological lesions that might be caused by different strains of the disease, i.e., his method of drawing up lesion profiles. Between the late 1950s and the early 1960s, researchers at Moredun and Compton had investigated detailed pathological changes in the scrapie-affected brain.[33] From those studies, researchers had drawn up several pictures of the pathological changes – particularly grey matter vacuolation – occurring in the brain of affected mice. Dickinson and his team suspected that the severity and distribution of vacuolation might vary from one strain of scrapie to

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[31] **Dickinson, A. G.** (1998) *Transcript 31 of the BSE Inquiry, t31* (London: The BSE Inquiry): 4-5

[32] The ME7 agent is one of scrapie strains that was isolated by Ian Zlotnik in 1963 [**Zlotnik, I., J.C. Rennie** (1963) 'Further observations on the experimental transmission of scrapie from sheep and goats to laboratory mice' *Journal of Comparative Pathology* **73**: 150]. This agent originated from the brain and spleen of a natural scrapie in Suffolk sheep at Moredun. It has some advantages for the purpose of genetic investigation: firstly, it produces clear-cut pathological changes; secondly, it shows clear symptomatic signs of scrapie, e.g., jerky movement, muscular tension of the body, and so forth. This agent has been used by the Edinburgh group for twenty years, and became one of the important agents for genetic investigations.

[33] **Zlotnik, I.** (1957) 'Vacuolated neurones in sheep affected with scrapie', *Nature* **179** (6 April 1957): 737; **Zlotnik, I.** (1957) 'Significance of vacuolated neurones in the medulla of sheep affected with scrapie', *Nature* ***180***(24 Aug. 1957): 393-394; **Zlotnik, I.** (1958) 'The histopathology of the brain stem of sheep affected with natural scrapie', *Journal of Comparative Pathology* ***68***: 148-165; **Zlotnik, I. and J. C. Rennie** (1962) *op. cit.* note 14; **Pattison, I. H. and K. Smith** (1963) 'Histological observations on experimental scrapie in the mouse', *Research in Veterinary Science* ***4***: 269-275

another. One of the pathologists in Moredun, Hugh Fraser,[34] established a tool for quantifying variations in the pathology, which is called "lesion profile". According to Kimberlin, "by quantitising the severity of vacuolation in nine narrowly defined areas of the brain, a sensitive system has been developed for studying the agent–host interactions".[35]

Transverse sections of brain are stained, and scored on a 0-5 grading in such a way as to eliminate subjective bias as far as possible. The scoring is based upon simple observations of the pathological severity: mild, severe, moderate severe, and so forth.[36] Hugh Fraser and Alan Dickinson then defined scores for the lesion density as follows:

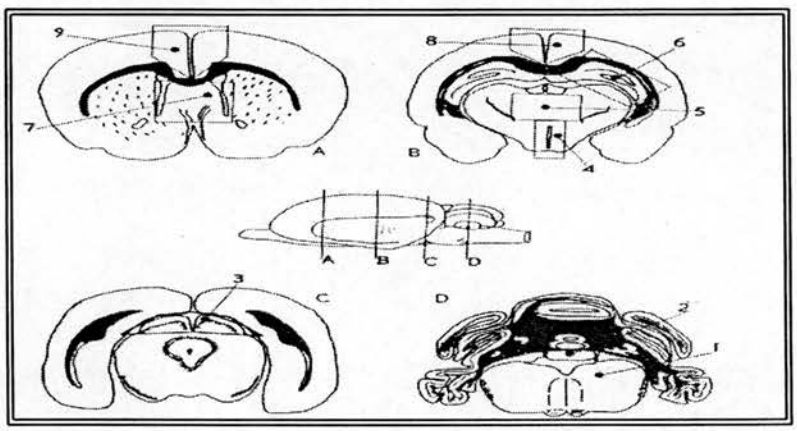

Figure 1: The positions used for scoring the lesion density in scrapie in the mouse. 1: medulla; 2. cerebellum; 3. mid-brain; 4: hypothalamus; 5: thalamus; 6: hippocampus; 7: paraterminal body; 8 & 9: cerebral cortex.[37]

1: a few vacuoles, widely and unevenly scattered
2: a few vacuoles evenly scattered

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[34] Hugh Fraser is a veterinary pathologist; he did his first degree at the Royal Veterinary College in London, and trained neurological disease at Cambridge. He had been involved in scrapie research since the mid-1950s. At the time, Ian Zlotnik mainly undertook the histopathological research at Moredun. In 1966, however, Zlotnik resigned from the head of the neuropathology section in Moredun. In his place, Hugh Fraser joined the Moredun-ABRO unit. He finished his PhD at the University of Edinburgh in 1971. He was head of experimental pathology at NPU until retirement in 1995. In the series of genetic experiments at the Moredun-ABRO unit, experimental pathology plays a crucial role in investigating the host/agent relations. Since the mid 1960s, his role in the Moredun-ABRO unit and in NPU was as significant as that of Alan Dickinson.

[35] **Kimberlin, Richard** (1976) *op. cit.* note 22: 14

[36] **Fraser, Hugh** (1999) Interview with author (Edinburgh: 30 June 1999)

[37] *Ibid.*, 304

3: moderate numbers of vacuoles, evenly scattered
4: many vacuoles with some confluence
5: dense vacuolation with most of field confluent[38]

These experimental methods proved highly successful. By the mid-sixties, Dickinson and his colleagues were able to identify and isolate nine different strain of the scrapie agent (ME7, 22A, 22C, 22L, 22M, 139A, 79A, 79V, and 80V: see Figure 2). Each was characterised by a particular combination of incubation time, pathological profile and preference for particular kinds of host mice. Moreover, each strain was stable in these characteristics over successive inoculations from one mouse to another.[39]

This experimental achievement involved an enormous standardisation of method. Before the 1960s, scrapie research was hampered by natural variation in experimental materials. The experimental transmission of scrapie into mice in 1961 by Richard Chandler was a major advance towards overcoming such problems. At Moredun, Dickinson and his colleagues focused on standardising various aspects of the experimental system: control of dose, measurement of infectivity, constructing optimal inbred mice, measurement of incubation time, and lesion profile. These systematic endeavours also enabled them to elicit very specific phenomena with a high degree of predictability, reproducibility and discrimination. At this stage, in the context of the Edinburgh group, the experimental work in scrapie research was changed from an "art" for a few "golden hands" to a standardised, simplified, and routine tool used by their own researchers.

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[38] **Fraser, H., A.G. Dickinson** (1968) 'The sequential development of the brain lesions of scrapie in three strains of mice', *Journal of the Comparative Pathology* **78**: 302

[39] Although the actual experimental procedure looks simple, researchers had first to passage each strain through many generations of mice in order to ensure genetical specificity. For example, to obtain the short ME7 incubation period strain, Dickinson's team had to breed for over 40 generations. They had used approximately 4,000 mice in about 400 experiments over 12 years. [**Outram, G. W.** (1976) 'The pathogenesis of scrapie in mice', R. H. Kimberlin (ed.), *Slow Virus Diseases of Animals and Man* (Amsterdam: North-Holland Publishing Co.): 338]

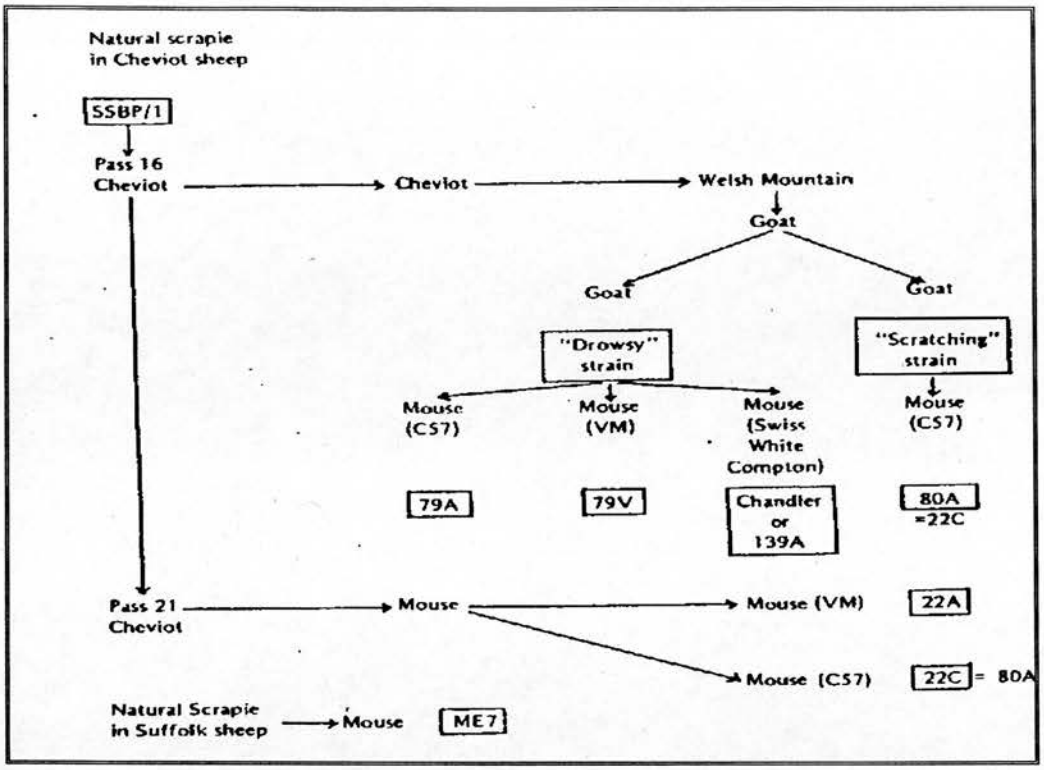

Figure 2: Origin of Various Scrapie Agents Isolated in the UK[40]

5. Elucidating the nature of the mouse genes responsible for variation in incubation time

Having demonstrated the involvement of host genes in scrapie infection, Dickinson's group began a series of experiments, published in 1968, which were designed to further elucidate the nature of the host genes responsible for determining the incubation periods of scrapie in mice.[41] In this project, the key variable observed was the scrapie incubation time. For this experiment, however, they kept the strain of scrapie constant (i.e. working with the scrapie strain ME7 throughout), and instead manipulated the genetic constitution of the mice in which the scrapie was cultivated. In other words, Dickinson and his colleagues were once again taking variation in incubation time due to the host genome as the signal, and eliminating the noise due to other sources of variation in incubation time.

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[40] **Kimberlin, R. H.** (1976) *op. cit.* note 22: 20

[41] **Dickinson, A. G., Veronica M.H. Meikle, H. Fraser** (1968) 'Identification of a gene which controls the incubation period of some strains of scrapie agent in mice', *Journal of Comparative Pathology* 78: 293-299

From the previous experiment in 1964, they observed that the incubation periods shown by the different mouse strains tended to fall into two distinct clusters: one group being relatively long incubation and the other relatively short. They speculated that mouse scrapie models could be divided into two groups: those showing "operationally short" incubation periods, and those showing "operationally long" ones. This had led Dickinson and his team to speculate further about the nature of the gene involved. As a result of the selection and inbreeding of the different lines of mice, and of the stability of the incubation period from one generation to another, it could be assume that each mouse line was homozygous for whatever genes were responsible for determining incubation period. The fact that these homozygotic lines tended to fall into just two groups suggested that the researchers were dealing with just two alleles of a single gene, which Dickinson and his colleagues suggested calling *Sinc*, which is an acronym for "*S*crapie *inc*ubation".[42]

Dickinson and Fraser set out to test whether or not this was the case. They proceeded along classical Mendelian lines, i.e., if they were indeed dealing with two alleles of a single gene, a simple series of cross-breeding experiments would produce a classic pattern of combination of these alleles. In the experiment of 1964,[43] Dickinson and Fraser selected two extreme strains of mouse line, which had long and short incubation with the ME7 agent: the first of these, RIII, was characterised by producing a very short incubation time when infected with scrapie strain, ME7. The RIII mouse stock demonstrates relatively short incubation periods with the ME7 strain of scrapie (20.8 - 21.5 weeks). If the single gene hypothesis was correct, this strain should be homozygous for the short incubation allele of the *Sinc* gene, which Dickinson denoted s7. The second line, VM,[44] was characterised by a long incubation period (24.6 - 40.0 weeks). Again, if the single gene hypothesis was correct, the VM mice should be homozygous for the prolonged incubation or p7 allele.

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[42] **Outram, G. W.** (1976) *op. cit.* note 39: 350

[43] **Dickinson, A.G., J.M.C. MacKay** (1964) *op. cit.* note 25

[44] A VM mouse was one of five partly inbred lines at Moredun (**Dickinson, A.G., J.M.C. MacKay** (1964) *op. cit.* note 25: 281).

Dickinson and his colleagues then crossed RIII with VM mice. In this case, if the hypothesis about the genetic constitution of these two strains was appropriate, this cross should produce a first filial generation (F_1) that was heterozygous for the two alleles, i.e., its genotype would be s7p7. Then, when mice from the F_1 generation were infected with scrapie, they showed an incubation time that was unimodal and intermediate between the two parental types (around 230 days). The results were consistent with the hypotheses, so Dickinson took this result to indicate that the F_1 generation was heterozygotic for *Sinc*, with no dominance shown by one or other allele.

Moreover, they performed two backcrosses using the F_1 generation, which also produced results consistent with this genetic constitution. Firstly, the F_1 generation was mated with RIII mice (backcross 1: B_{x1}). If their hypothesis was correct, then this would corresponded to crossing s7p7 x s7s7, and the progeny would be a mix of s7p7 (i.e. F_1 type) and s7s7. When mice from the progeny of this cross were infected with scrapie, they did indeed show a spread of incubation times which spanned the short and intermediate incubation times of RIII and the F_1 generation. In other words, the incubation period was distributed around 150-200 days. Secondly, likewise backcrossing F_1 generation with VM mice (B_{x2}), they would expect the progeny to be a mix of F_1 generation and VM type. When the progeny was infected with the agent, it showed that the incubation period distribution had a bimodal pattern (around 200 days and 300 days). In this case, the incubation period conformed even more clearly to their hypothetical genotypes, falling into a clear bimodal distribution corresponding to the VM and intermediate types.

Finally, when mice from the F_1 generation were crossed with each other, the incubation period of the resulting F_2 generation appeared to be trimodally distributed corresponding, as would be expected, to a mix of homozygous and heterozygous mice.

More detailed results of the experiments are shown in Figure 3, below:

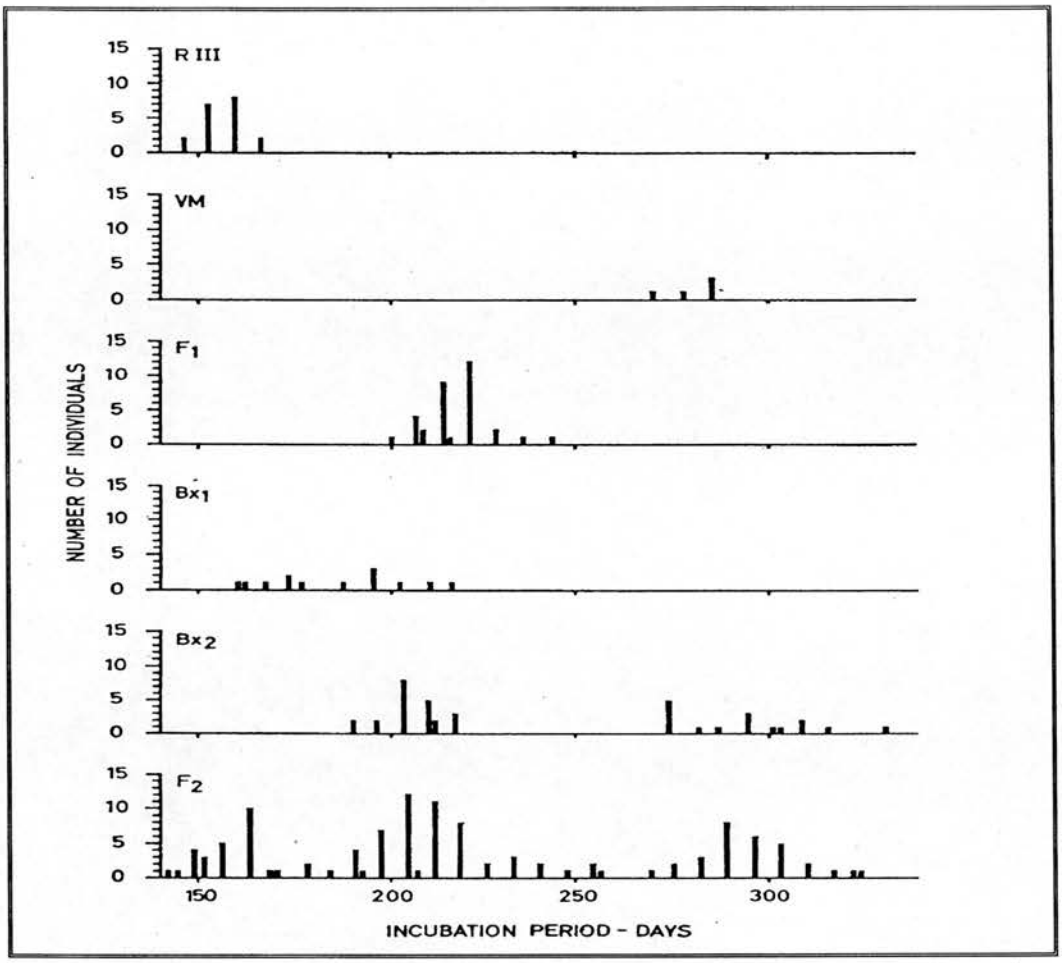

Figure 3: Distribution of incubation periods in parental, F_1, F_2 and backcross generations[45]

All of this is consistent with the hypothesis that they were dealing with two alleles of a single autosomal gene showing no dominance, and with two parental types that were homozygous for one of these alleles. This conclusion was further confirmed when the Edinburgh researchers looked at the pattern of pathological changes in the brains of VM, RIII, and F_1 mice infected with scrapie. The lesion profile in the two parental mouse strains was different, while the lesion profile in the F_1 mice was intermediate between those produced in VM and RIII mice.[46] As seen in the Figure 4, the pathological pattern of the first generation (F_1) is an intermediate form. This pattern is similar to the incubation period of F_1, which is intermediate between two parental strains (VM and RIII mice).

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[45] **Dickinson, A. G., Veronica M.H. Meikle, H. Fraser** (1968) *op. cit.* note 41: 295

[46] *Ibid.*, 296

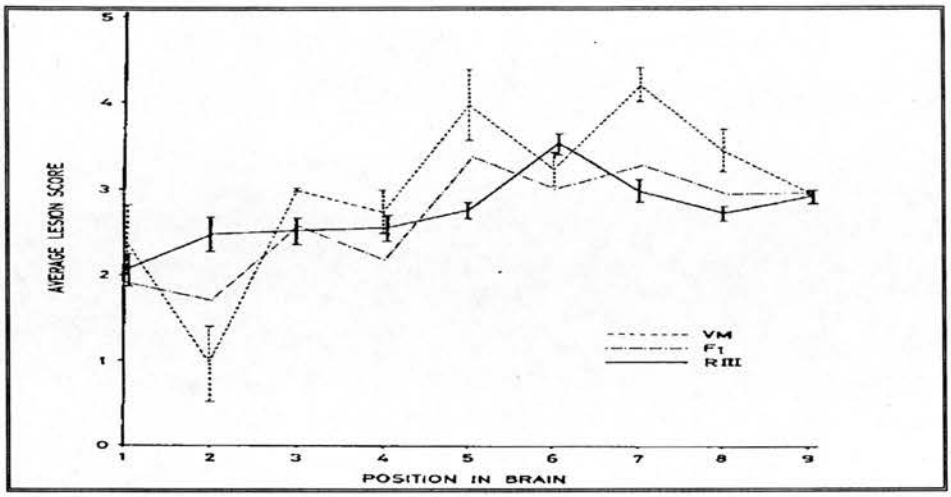

Figure 4: The intensity of the ME7 scrapie lesion density in nine regions of the brain in parental and F_1 generations.[47]

In conclusion, the Edinburgh researchers found strong evidence that a single host gene exerted a significant influence over the pathological development of scrapie in mice. Dickinson and his colleagues state that "the name *Sinc* is proposed for it, and the two alleles which show no dominance are designated s7 for the one which shortens the incubation period, and p7 for the one which prolongs it. The distribution and intensity of brain lesions are shown to be quite distinct in the two homozygotes, as represented by two mouse strains, and the heterozygote, as represented by the F1's cross".[48]

6. Demonstrating that the action of the host genes varies with different strains of scrapie agent

In 1969, Dickinson initiated a further experiment to investigate how the *Sinc* gene influenced the scrapie incubation period. The previous experiment had shown how *Sinc* affected the incubation time of scrapie strain ME7. In the new experiment, Dickinson looked to see if the same phenomena occurred when other strains of scrapie were inoculated into mice homozygous and heterozygous for *Sinc* called s7

[47] *Ibid.*, 296
[48] *Ibid.*, 299

and p7. Dickinson again used the VM mouse for his p7p7 homozygote, but this time replaced the RIII mouse with another strain, C57BL, that had since been shown to be homozygous s7s7.[49]

With most strains of scrapie, the patterns of incubation time observed in the three different mouse-lines (VM, C57BL, and F_1) were broadly similar to those observed with ME7 – i.e. a long incubation in p7p7 mice, a short incubation in s7s7 mice and an intermediate incubation time in s7p7 mice. This is the case with scrapie strains 22C[50], 22L, 79A[51], and 79V.

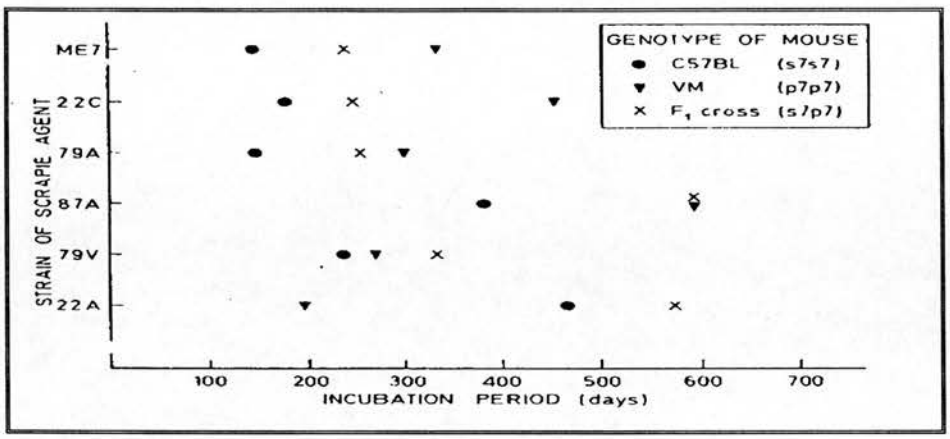

Figure 5: The variety of interactions between different strains of scrapie agent and the alleles of *Sinc* gene. The figure shows the incubation period of each agent in F_1 mice (s7p7) in relation to that found in the two parental strains, namely, C57BL (s7s7) and VM (p7p7).[52]

However, Dickinson and his team also noticed a further and rather intriguing phenomenon. With different scrapie strains, the precise degree of mixing of the incubation period observed in heterozygous s7p7 mice varied. As you can see in Figure 5, with the scrapie strain 22C, the incubation period in heterozygous s7p7 mice was closer to that in homozygous s7s7 mice than to that in homozygous p7p7 mice. In the case of 79A, by contrast, it was closer to the incubation in p7p7.

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[49] **Dickinson, A. G., Veronica M.E Meikle** (1969) 'Genetical control of the concentration of ME7 scrapie agent in the brain of mice', *Journal of Comparative Pathology* 79: 15-22

[50] The 22C agent is obtained from the transmitted mice of C57 stock by 21st passage of Cheviot sheep by Alan Dickinson [**Dickinson, A. G.** (1975) 'Scrapie in sheep and goats', R. H. Kimberlin (ed.) *Slow Virus Disease of Animal and Man* (Amsterdam, North-Holland Publishing Co.): 220]

[51] The 79A agent is isolated from the drowsy type of goats, which is transmitted from scrapie in the Cheviot sheep. When the scrapie in goats is transmitted into C57mice, then 79A strain is obtained. The agent was isolated by Dickinson. (See Figure 2; *ibid.*,220)

[52] **Kimberlin, R. H.** (1976) *op. cit.* note 22: 22

Furthermore, with the 87A strain, the incubation time in heterozygous s7p7 mice was identical with that in homozygous p7p7 mice.

Dickinson and his team interpreted this variability in terms of the genetic phenomenon of dominance. Dominance is the tendency for one allele of a particular gene to be expressed more strongly than another in heterozygous individuals. Thus, in cases where the scrapie incubation period in s7p7 mice tended towards that in s7s7 mice, as for instance with the 22C scrapie strain, Dickinson claimed that the s7 allele of *Sinc* was partially dominant. On the other hand, in the case of scrapie strain 87A, where the incubation period in s7p7 mice was the same as in p7p7 mice, Dickinson read this as indicating that the p7 allele of *Sinc* was completely dominant. Moreover, in the case of scrapie strain 79V, the p7 allele showed ***over***dominance where the incubation time in s7p7 mice exceeded that in p7p7. The Edinburgh group were intrigued by the fact that the degree of dominance of the two alleles of the mouse gene *Sinc* varied depending upon what strain of scrapie the mice were infected with.

Even more intriguing was the fact that, with scrapie agent 22A, the effects of *Sinc* alleles s7 and p7 were completely reversed. In C57BL mice, homozygous for s7, the incubation period was longer than in VM mice, homozygous for p7 – the opposite of what occurred with, for instance, scrapie strain ME7 (see Table 1). This implied that the presence of the s7 allele of *Sinc* appeared to prolong the incubation period where the p7 allele tended to shorten it. Furthermore, in heterozygous s7p7 mice, the incubation time was even longer than in homozygous s7s7 mice, i.e. the s7 allele displayed over-dominance.

Agent	Mouse Strain	
	C57	VM
ME7	165	299
22A	443	205

Table 1: Relative incubation periods in C57 and VM[53]

[53] **Dickinson, A.G., Veronica H.M. Meikle** (1969) *op. cit.* note 49: 222. There are also clinical differences between the two strains; mice injected with 22A agent displayed ***chronic***

Dickinson and Meikle speculated that there were two possible explanations for these peculiar phenomena. On the one hand, it was possible that other host genes besides *Sinc* might play a role in determining the incubation period of some strains of scrapie. On the other hand, it was possible that the different incubation time effects were solely due differences in the various strains of scrapie agent and the way they interacted with the host *Sinc* gene. His next experiment was designed to test whether the first of these hypotheses was true.

7. Eliminating the possibility that other mouse genes besides *Sinc* are involved

Dickinson was aware that his conclusions regarding the variance in dominance relations between the different *Sinc* alleles in the presence of different strains of scrapie were entirely dependent on the truth of an important presupposition, namely that no other mouse genes were involved, at least to any great extent, in determining the incubation period of the scrapie agent. It was of course perfectly possible that other host genes were involved, and were responsible for instance for the displacement of the intermediate heterozygous incubation times towards one homozygous extreme or the other, or for the apparent reversal of the influence of the s7 and p7 alleles in the case of the scrapie strain 22A. Consequently, before proceeding to reason further towards an explanation of these various phenomena, around 1970, Dickinson and his technician Meikle undertook a further experiment to investigate whether or not other genes besides *Sinc* might be implicated in determining scrapie incubation time.[54]

In the previous experiment, Dickinson had only looked at the incubation period of different scrapie strains in the parental mouse types, VM and C57BL, and in the F_1 generation produced by crossing these two mouse types. For each strain of scrapie,

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progressive ataxia, in contrast with ME7-injected ones of the same stock, when the usual syndrome was a ***progressive lethargy*** (*Ibid.*, 216)

these three mice populations had produced three distinctive incubation periods, which Dickinson attributed solely to the influence of parental mouse genotypes, s7s7, p7p7 and the heterozygote s7p7. If only the *Sinc* gene was indeed involved, then further crosses would produce F_2 and further generations which would consist of mixtures of the three genotypes s7s7, p7p7, and s7p7, and would consistently produce the same trimodal distribution of incubation periods corresponding to these three mouse genotypes. If, on the other hand, another mouse gene was involved in determining the scrapie incubation period, then ordinary Mendelian recombination would mean that the F_2 and subsequent generations of mice would include a much larger number of relevant genotypes. If scrapie was inoculated into these mice, it would result in a distribution of incubation times that would *not* correspond to the three earlier mouse genotypes, i.e., the two parental and the F_1 genotypes.

The experiment was conducted as follows: Dickinson carried out the experiment using VM and C57BL for p7p7 and s7s7 homozygotes, and inoculating these and subsequent generations of mice with the ME7 and 22A strains of scrapie. They claimed that "it was known from the previous work that the three genotypes s7s7, p7p7 and s7p7 could be distinguished for the F_2 generation in terms of the response to ME7 scrapie and, if the same gene controls the response to the 22A strain, the results for the F_3 families should be predictable from the parental genotypes".[55] Dickinson found that for both strains of scrapie, the distribution of incubation times in the F_2 and F_3 generations of mice did indeed appear to follow a trimodal combination of the incubation times observed in VM and C57BL and their F_1 hybrid (see the third diagram in Figure 5). The experimental results are as follows:

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[54] **Dickinson, A. G., Veronica M.H. Meikle** (1971) 'Host-genotype and agent effects in scrapie incubation: change in allelic interaction with different strains of agent', *Molecular and General Genetics* **112**: 73-79

[55] *Ibid.*, 73

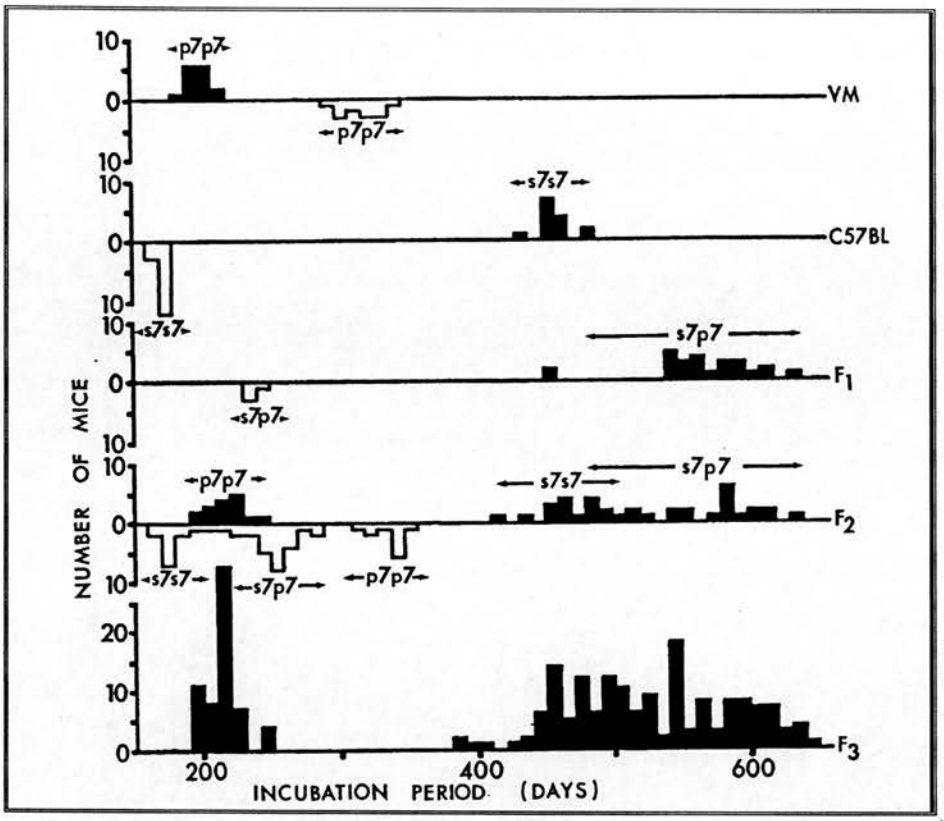

Fig. 5. Incubation period of two scrapie agents in inbred, F_1, F_2 and F_3 mice following intracerebral injection. Mice injected with 22A agent are shown as solid histograms, those injected with ME7 are shown as open histograms. The *Sinc* genotypes are given adjacent to the appropriate modal groups.[56]

In conclusion, Dickinson and his colleagues saw this experiment as indicating that only a single mouse gene, *Sinc*, is responsible for determining the incubation period of both the ME7 and the 22A strains of scrapie in mice. They went on to confirm this result in a wide range of mouse stocks, including A2Gf/Lac, BALB/cf/Lac, BRVRf/Sr, BSVS/Sr, C57BL/fa, C3Hf/Lac, DBA/2f/Lac, EM/Dk, LG/J, LM/Dk, MM/Dk, NMRIf/Lac, RIII/Fa, SM/J, VM/Dk, and 129f/Lac. In no case were results obtained that could not be explained by the single gene-two alleles hypothesis.[57]

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[56] *Ibid.*, 75. These results also confirmed the phenomena of absence of dominance with ME7 an overdominance with 22A.

[57] **Dickinson, A.G., Veronica H.M. Meikle,** unpublished work; **Dickinson, A.G., Veronica H.M. Meikle** (1971) *op. cit.* note 54: 77. When many other experiments were conducted with various scrapie agents investigating the pattern of incubation period, the main pattern was identical to ME7 or 22A. No agent has been found with a shorter incubation in F_1 than in either parent or even as short as in the shorter parent.

8. The replication site theory

By the mid-seventies, Dickinson and his colleagues at Edinburgh had accumulated a very rich body of experimental knowledge and experience of the scrapie agent and its behaviour in different lines of inbred mice. This included the isolation and characterisation of a number of different strains of scrapie agent. Since the early 1960s, the team had isolated at least 14 different strains of the agent. Moreover, they identified a mouse gene, *Sinc,* which was responsible for controlling the scrapie incubation period, as well as identifying a number of lines of inbred mice homozygous for one or other of the two alleles, s7 and p7. It also included strong evidence that while the incubation time of some strains of scrapie was shortened in mice carrying allele s7 and prolonged in those carrying p7, with other strains of scrapie these effects of the mouse genotype were reversed. Finally, it included strong evidence that the dominance relations between s7 and p7 in mice heterozygotic for *Sinc* varied in the presence of different strains of the scrapie agent.

At the time, Dickinson and his colleagues felt that they were in a position to begin formulating a theoretical model of the interaction between the scrapie agent and its host that would bring together and explain all those experimental results. They began by considering the fact that genetically-determined aspects of the host organism evidently played a significant role in affecting the rate at which the scrapie agent could replicate and ultimately cause disease symptoms in the host. In speculating what that role might be, they regarded the variability of the dominance relations of the two alleles of the *Sinc* gene as particularly suggestive. The researchers believed that the variations in gene action were dependent upon allelic interactions between the agent and the host genotypes (p7, s7 and s7p7).

The simplest kinds of dominance relations obtain in cases where one allele of a gene codes for a faulty, and therefore inactive, version of an enzyme, while the other allele codes for the active version. Organisms homozygotic for the faulty version of the gene will be unable to produce an active version of that enzyme, so will lack the function that it fulfils. On the other hand, organisms homozygotic for the normal allele will be able to produce an active enzyme, and so will display that function. In

the case of heterozygotes, a single copy of the functional gene exists, so they too will be able to produce the active enzyme. In this case, the functional allele will display dominance over the faulty one. The degree of dominance will then depend on further factors. In cases where a single copy of the normal allele is sufficient to produce enough of the relevant enzyme for full functionality, then heterozygous organisms will be functionally identical to those with two copies of the normal allele, thus complete dominance will obtain. On the other hand, in cases where the functionality of the enzyme depends upon the quantities in which it is produced, and where possession a single copy of the relevant gene results in the production of less enzyme than in organisms possessing two copies, then functionality will be compromised in the heterozygote and dominance will be incomplete.

In the case of the *Sinc* gene, however, the dominance relations were rather more complicated than could be explained on this simple activity/inactivity model. In particular, the model cannot explain the phenomenon of *over*dominance exhibited in the *Sinc* gene under certain circumstances. Recall that in mice infected with scrapie strains 22A and 79V, the incubation period in the heterozygote is longer than in mice homozygous for the prolonged incubation allele (i.e. s7 in combination with 22A, and p7 with 79V), rather than intermediate between the long and short incubation homozygotes. Dickinson thought that this phenomenon was the most important piece of information about the scrapie replication process. Dickinson's team therefore reasoned that, in the case of the *Sinc* gene, the proteins coded by the s7 and p7 alleles must somehow be capable of *interacting* when both are present (i.e., in the heterozygote), so as to bring about a scrapie incubation period that is longer than when just one or other of the proteins is present.[58] This overdominance, in other words, indicates that the two-allele products do not act independently of one another.[59] According to Moira Bruce, one of Dickinson's collaborators:

> I think that two proteins [as genetic products] cannot be acting independently. They are interacting in some way. Two alleles of gene, each produces its own protein and that is

[58] **Dickinson, A.G., Veronica H. M. Meikle** (1971) *op. cit.* note *54*: 77

[59] **Dickinson, A. G.** (1975) 'Host-pathogen interactions in scrapie', *Genetics: Supplement* 79: 390

> what you end up with; it's not just this product and that product acting independently, which means that there is some sort of interaction between those two products.[60]

In considering how this interaction might occur and what it might involve, Dickinson and his team set their genetic findings against a backdrop of more general thinking about, and investigation into, the infectious nature of scrapie, its pathological manifestations, and the immunological and biochemical properties of the infectious agent.

Around the same time, there was a lot of interest in various kinds of anomalous diseases, particularly what were seen to be virus-related diseases. The thing about viruses is that they are not living organisms as such: they consist of a relatively small genome of nucleic acid (DNA or RNA) wrapped in a protein coat. However, the viruses do not possess the kind of metabolic machinery that enable living cells and bacteria to undertake various vital functions, including self-replication. Rather, viruses can only reproduce themselves by parasitising the metabolic machinery of another living organism, and turning that machinery to production of new copies of their own genome and coat proteins. It should be noted that the genomic and protein structures of some viruses had been relatively well characterised by the early 1970s. However, such work was also turning up a number of interesting variants on the normal pattern of viral structure and activity. The recent discovery of an infectious "viroid" was a good case in point. This was just a short length of naked DNA, not even protected by a protein coat, which nonetheless was able to parasitise plant cells and turn them to the work of replicating itself.[61] This led some scientists to speculate that the scrapie agent might also be viroid.[62]

Dickinson and his colleagues speculated that the scrapie agent might be something in effect intermediate between a viroid and a virus. The agent might include a relatively small genome, which is replicated when the scrapie agent replicates in the host. It might also include a protective protein coat, but this coat

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[60] **Bruce, Moira E.** (1999) Interview with author (NPU, Edinburgh: 9th June, 1999)

[61] **Diener, T.O.** (1971) 'Potato spindle tuber virus IV', *Virology 45* (2): 411-428

[62] **Diener, T. O.** (1972) 'Is the scrapie agent a viroid?', *Nature New Biology* 235 (16 Feb.1972): 218-219; **Diener, T. O.** (1973) 'Similarities between the scrapie agent and the agent of the potato spindle tuber disease', *Annals of Clinical Research* 5: 268-278

could consist, not of specifically viral proteins, but of host proteins. In other words, the genome of the infectious agent might not include the genetic information needed to manufacture its own coat proteins. Rather the agent uses protein the genetic instructions for which derive from the host genome. They called this putative new infectious agent a "virino", to distinguish it from ordinary viruses.[63] The virino's own nucleic acids would be tightly complexed to the host protein. Thus, the virino would not need to be a large size. The virino genome would then have only two functions - the ability to use host processes for its replication, and the acceptance of a coating of host molecules for its protection and infectivity.[64] Dickinson and his colleagues got the name "virino" from the Italian physicist, Enrico Fermi, who suggested that a small nuclear particle shared some characteristics with the neutron. He called this little neutron-like particle a "neutrino". Therefore, Dickinson calls the infective agent of scrapie a virino. According to the science writer Richard Rhodes, "[Dickinson] recalls Peter Medawar's quip to define his virino informally as 'bad news securely wrapped in somebody else's protein'".[65]

The virino hypothesis is attractive because it serves to explain a number of the anomalous pathological and biochemical properties of the scrapie agent. The protective coat of host protein is consistent with its anomalous properties, including its resistance to viricidal and antibacterial treatments, and the immunological inertness that was one of basic themes of the original classification of slow infection.[66] According to James Hope, who worked with Dickinson:

> The virino model more closely mirrored Sigurdsson's original insight – "one...suspects that there is no effective immunity response in the slow infections, which seem to progress unhampered for long periods of time until they kill. If immunity develops at all, it must be a very ineffectual one. Perhaps the infectious agent is so well adapted to its host, so well camouflaged, that it has to some extent eliminated its own species

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[63] **Dickinson, A. G., G. W. Outram** (1988) 'Genetic aspects of unconventional virus infections: the basis of the virino hypothesis', Greg Bock & Joan Marsh (eds) *Novel Infectious Agents and the Central Nervous System13* (Chichester: John Wiley & Sons): 63-83

[64] **Dickinson, A. G.** (1982) 'Scrapie: strategies, stalemates, and successes', *Lancet* **1** (29 May 1982): 1222

[65] **Rhodes, R.** (1997) *Deadly Feast: Tracking the Secrets of a Terrifying New Plague* (New York: Simon & Schuster): 164

[66] **Sigurdsson, B.** (1954) *op. cit.* note 16

specificity in the immunological sense?" In the virino, the Sinc gene product – a host protein – provides the "camouflage."[67]

In this sense, the virino can explain why some anomalous features arise. For one thing, the idea that the protective coat is made up of host proteins explains why there is no observable immune response to scrapie infection. The immune system of the host fails to recognise the scrapie agent as an invader, since the small amount of foreign genomic material is wrapped in and protected by the proteins identical to proteins proper to the host itself. For another thing, the idea that replication of the scrapie agent involves commandeering the host's own protein, coded for by the host genome, provides a way of thinking about the peculiar phenomena exhibited by the host gene *Sinc*.

The most peculiar and suggestive aspect of the behaviour of the *Sinc* gene, as we have seen, is the fact that under certain circumstances those alleles that lead to prolongation of the incubation time of scrapie can exhibit overdominance over the short incubation alleles, and that this implies some kind of interaction in the heterozygote between the two different alleles or their protein products. Dickinson and his colleagues claimed that this interaction might be explained if we suppose that the host protein coded by *Sinc* is involved in some way in the replication of the infectious agent, and that the reproduction of the scrapie agent depends upon the combination of a number of such protein molecules into multimers. In the case of mice homozygous for *Sinc* (whether s7s7 or p7p7), these multimeric structures would be homomeric, i.e., they would consist of a number of identical protein chains. However, in the case of heterozygous mice, these multimers would be heteromeric, i.e., they would consist of two different kinds of protein monomers, one coded by alleles s7 and the other by p7. In such cases, hypothesised Dickinson and his colleagues, the functionality of the protein assemblages might be altered in such a way as to bring about a particularly lengthy scrapie incubation period.

The simplest case of such interaction would of course occur if the host gene *Sinc* was actually responsible for providing the genetic template for the coat protein, and

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[67] **Hope, J.** (1994) 'The nature of the scrapie agent: the evolution of the virino', *Annals of the New York Academy of Sciences 724*: 283-284

the protein coat was itself the hypothetical multimeric structure. Differences in incubation period between s7s7 and p7p7 homozygotes might then be explained if the protein coat coded for by one allele could be produced or assembled into a homomeric protein coat more quickly or readily than the protein coded for by the other. More importantly, the phenomenon of overdominance might be explained if for some reason it proved particularly difficult to combine the two different types of coat protein, one coded by s7 and the other by p7, into a heteromeric coat structure.[68] They speculated that agent replication must be very limited, otherwise the small proportion of "quick" homomers would be sufficient to give heterozygote incubation periods at least intermediate between the parental types, or even as short as in the quicker homozygote.[69] However, the experimental data indicated no such case of shorter incubation time than the parental types.

The theory of the dependency of the infectious agent on the activities of the host genome for its own replication also provided Dickinson with a way of thinking about, and offering a speculative explanation for the relatively long incubation and slow development of scrapie in the host. Dickinson supposed that some aspect of the structural material or metabolic machinery necessary for replication of the scrapie agent, and provided by the host, exists in relatively short supply in the host. Dickinson called this the "replication site" of scrapie. Consequently, the scrapie agent has to somehow colonise, and take control of the replication site to replicate itself, but the speed at which this process can take place is limited by the availability or assimilability of the replication site.

The idea of a limited availability of replication sites was confirmed by several experiments. One of the main pieces of evidence came from a large series of experiments in which two different strains of the agent had been shown to

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[68] **Dickinson, A. G.** (1975) *op. cit.* note 50: 390; **Dickinson, A. G., H. Fraser** (1975) 'Scrapie: pathogenesis in inbred mice: an assessment of host control and response involving many strains of agent' in V. T. Meulen & M. Katz (eds), *Slow Virus Infections of the Central Nervous System* (New York: Springer-Verlag): 11; **Dickinson, A. G., G.W. Outram** (1979) 'The scrapie replication-site hypothesis and its implications for pathogenesis', S.B. Prusiner & W. J. Hadlow (eds) *Slow Transmissible Diseases of the Nervous System* 2 (London: Academic Press): 18

[69] **Dickinson, A. G., G.W. Outram** (1979) *op. cit.* note 68: 18

compete.[70] Mice of a particular *Sinc* genotype were inoculated with a strain of agent which has "slow" pathogenesis in that genotype, and then, after an interval, with an operationally "quick" strain of agent. The interpretation of these experiments relied on histological criteria to determine which of the agents killed the mice.[71] Dickinson and his colleagues observed that there was a kind of competition between the two operationally different agents. The overall incubation period increased. For instance, if the 22A agent was inoculated into RIII mice (22A in RIII mice produces a long incubation), and after a certain interval the 22C agent was injected (22C with RIII mice produces a short incubation), then they found that the 22A agent killed the host. The researchers hypothesised that the replication site was being blocked by the first-injected agent (22A), even though the second agent (22C) may be a much quicker agent than the first one.[72] In this experiment, it was concluded that the slower agent (22A) was able to occupy all available sites so that the second agent (22C) was excluded from participation in the disease, and must have been either sequestered, excreted or degraded. This experiment implied support for the scrapie replication site hypothesis. Dickinson and his colleagues claimed that "agent competition is therefore envisaged as resulting from the agent injected first, having had the opportunity to occupy some or all the available sites, and thus blocking the access of agent injected later. The total efficiency of blocking achieved in the experiment also indicates that the rate of site turnover is low."[73]

By the late 1970s, then, on the basis of this lengthy series of experiments, the Edinburgh researchers had formulated a hypothetical account of the nature of the scrapie agent and its means of replication that accounted for many of the peculiar features of the disease. First, the agent included a small genome, of which several distinct strains existed. This genome depended on the host organism's own genetic machinery for its replication, which apparently took place at a limited number of so-

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[70] **Dickinson, A. G., H. Fraser, V.M.H. Meikle, G.W. Outram** (1972) 'Competition between different scrapie agents in mice', *Nature-New Biology* 237 (21 June, 1972): 244-245

[71] *Ibid.*, 19

[72] **Dickinson, A. G., H. Fraser, I. McConnell, G.W. Outram, D. I. Sales, D. M. Taylor** (1975) 'Extraneural competition between different scrapie agents leading to loss of infectivity', *Nature* 253 (13 Feb. 1975): 556

[73] *Ibid.*, 556

called replication sites. Second, the scrapie genome was protected by its close association with protein molecules that were coded, not by the scrapie genome itself, but by a host gene called *Sinc*. This accounted both for the peculiar interactions between different scrapie strains and different host genotypes, and for the striking chemical resistance and immunological invisibility of the agent.

9. Summary

In this chapter, I have described a series of experiments performed by Alan Dickinson and his colleagues at the Moredun-ABRO unit during the 1960s. The experimental projects mainly dealt with genetic and pathological features of scrapie. After constant failure of conventional physico-chemical attempts to isolate the disease agent in the 1950s, some scientists proposed that scrapie was a hereditary disease, due to a recessive gene. However, collaborative research at the Moredun Institute and Animal Breeding Research Organisation (ABRO) from 1957 confirmed that the disease was in fact a contagious disease.

Dickinson and Fraser launched a full-scale genetico-pathological project to clarify the mechanisms of scrapie replication in the early 1960s. The new project suggested a new way of understanding the disease. Whereas conventional approaches had sought to isolate the disease agent, Dickinson's approach employed biological methods to examine the nature of interactions between the agent and host genome. Over nearly 15 years, their genetic and pathological work revealed many peculiar characteristics of the agent. In particular, the researchers showed how one autosomal host gene, called *Sinc*, influences the process of scrapie replication. The scrapie agent contained virus-like genetic information, but the agent hijacked the host for the replication.[74] Once the scrapie agent finds the right site for replication, the host gene, *Sinc*, produces protein which was the replicating scrapie genome. That is why the host immune system fails to detect the invasion of the exogenous

[74] Dickinson's concept of the replication site, and of the scrapie genome's appropriation of the host's genetic machinery for its own replication, appears to have been informed by the fundamental work of Francois Jacob and Jacques Monod during the 1960s and 1970s on the regulation of gene action and transcription. See **Hope, J.** (1994) *op. cit.* note 67: 282

agent. The scrapie agent was thus different from conventional viruses, leading Dickinson to propose that it should instead be called a ***virino***.

Since the first modern investigation on scrapie began in the 1910s, the scientific community had been struggling to understand the disease. In this situation, the Edinburgh researchers' experimental results were hailed as a remarkable achievement.[75] At the same time, however, other work was being conducted that some scientists, at least, considered to be at odds with Dickinson's virino hypothesis. In the next chapter, another line of experimental observations with biophysical and molecular methods will be discussed.

[75] **Hunter, G. D.** (1972) 'Scrapie: a prototype slow infection', *The Journal of Infectious Diseases* *125*(4): 427-40

Chapter 4 - Radiobiological Research at the Institute for Research into Animal Diseases (IRAD), Compton, 1964-1978

1. Introduction

Whilst Dickinson and his team at the Moredun-ABRO unit carried out a series of experiments to explore the genetic aspects of scrapie, another group of microbiologists and biophysicists researched on scrapie at the Institute for Research on Animal Diseases (IRAD), Compton. Their experimental results and speculations on the nature of the puzzling disease were at odds with those generated by their colleagues north of the border.

On the basis of radiobiological results, the research group at Compton speculated that the scrapie agent might not contain genetic material, i.e. nucleic acid, which by that time was generally regarded as the blue print of all life forms on earth. This experimental result was contradictory to what Dickinson and his group claimed, based on their genetico-pathological work. The experiment at Compton was led by Tikvah Alper, a radiobiologist at London's Hammersmith Hospital, and Dr. D.A. Haig and M.C. Clarke of the IRAD. Alper and her colleagues exposed samples of scrapie-infected mouse brain to radiation in order to estimate the molecular weight of the agent. This experiment relied on the so-called "target theory" in radiobiology, which was based on the relationship between the intensity of the electron doses needed to denature the agent and the size of the target molecule. The researchers concluded from their experiments that the scrapie agent was much smaller than conventional viruses, and that the agent might be able to replicate without itself containing nucleic acid.[1] Further series of experiments reinforced their support for

[1] **Alper, T., W.A. Cramp, D.A. Haig, M.C. Clarke** (1967) 'Does the agent of scrapie replicate without nucleic acid?', *Nature* ***214***(20 May, 1967): 764-766

the latter conclusion.[2] This conclusion was a striking departure from the conventional idea that nucleic acid was essential for biological replication. [3]

In this chapter, I will describe the radiobiological experiments conducted by Alper's group, and how they reached the conclusion that the agent did not contain any genetic material. In the context of the 1960s, this radical claim met with hostile reactions and criticisms. Nonetheless, the IRAD researchers proceeded to formulate hypotheses about how the infectious process might occur without genetic material. These hypotheses were intended to explain the anomalous features of the scrapie agent.

2. The IRAD and early work on scrapie

The Institute for Research on Animal Diseases (IRAD) at Compton was established in 1937 as one of the first field stations of the Agricultural Research Council (ARC). The original aim of the field station was to conduct large-scale field experiments on contagious diseases in cattle. A government committee had recently argued that the best approach for conducting such studies was to establish a "farm centre" under the direct control of the Council.[4] In 1937, the ARC purchased the Compton Manor Estate on the Berkshire Downs. The property consisted of 1,500 acres with suitable buildings and a herd of 400 diary cattle with a good health history.[5] The farm centre was established under the direction of Major G.W. Dunkin. The Field Station had two main objectives: firstly, to provide isolated accommodation for cattle and other farm animals; and secondly, to breed farm and

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[2] **Alper, T.** (1972) 'The nature of the scrapie agent', *Journal of Clinical Pathology-supplement* **6**: 154-155; **Alper, T., D.A. Haig, M.C. Clarke** (1978) 'The scrapie agent: evidence against its dependence for replication on intrinsic nucleic acid', *Journal of General Virology* ***41***: 503-516

[3] **Crick, F.** (1970) 'Central dogma of molecular biology', *Nature* 227 (8 Aug.1970): 561-563

[4] In 1936, a committee called the "Contagious Abortion Committee" under the Chairmanship of Joseph Arkwright, investigated research on animal contagious diseases in many research institutions. The committee published a report, called the "Major Committee Report", in which they recommended setting up a farm centre to concentrate on research on animal diseases. [see **Henderson, William** (1981) 'British agricultural research and the Agricultural Research Council: a personal historical account', G.W. Cooke (ed.) *Agricultural Research 1931-1981: A history of the Agricultural Research Council* (London: Agricultural Research Council): 3-99]

[5] *Ibid.*, 29

laboratory animals of known health history for experiments at Compton and to provide a surplus of animals for other institutes.[6] In 1963, the name of the field station was changed to the present "Institute for Research on Animal Diseases".

Following the death of Major Dunkin in 1941, William Gordon, who was the main figure in the famous "louping-ill incident"[7] in the 1930s, was appointed Director. He was very interested in scrapie research, and as soon as the opportunity arose in the mid-1950s, as a result of renewed US and UK government concern, he resumed scrapie research in Compton.[8] In this context, in 1957, as described in the previous chapter, Gordon conducted a large-scale experiment investigating the different degrees of susceptibility and resistance to the disease. This experiment became known as the "twenty four breed experiment".[9]

The institute consisted of four major departments: biochemistry, functional pathology, microbiology and pathology. Apart from Gordon's susceptibility work, each department conducted its own experimental projects on scrapie. First, researchers in the pathology department carried out a relatively long-term project on transmission of sheep scrapie into goats. In this project, Pattison and Mills not only demonstrated that scrapie in sheep could be transmissible into goats,[10] but also showed, more interestingly, that scrapie in sheep and goats had two forms: drowsy

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[6] **IRAD** (1967) *Agricultural Research Council, Institute for Research on Animal Diseases: Report* (Compton: IRAD): 7

[7] **Gordon, W. S.** (1946) 'Advances in veterinary research: louping-ill, tick-borne fever, and scrapie', *The Veterinary Record* **58**(47): 516-525. For more detailed explanation of the accidental experiment, see chapter 2, 'Background history of scrapie research, 1750-1960'.

[8] **Pattison, I. H.** (1992) 'A sideways look at the scrapie saga: 1732-1991', S. B. Prusiner, J. Collinge, J. Powell & B. Anderton (eds), *Prion Diseases of Humans and Animals* (New York: Ellis Horwood): 16; The commencement of scrapie research at Compton was decided when some sheep exported from Britain developed scrapie in Canada, United States, Australia and New Zealand. Those countries placed an embargo on British sheep, and this closure of export markets created calls for control by Government. The scrapie research was set up as part of a long-term programme, which had received financial support from the United States Department of Agriculture (USDA) by Public Law 480 funds. For more detailed situation, see the chapter 2.

[9] **Gordon, William S.** (1964) 'Review of work on scrapie at Compton, England, 1952-1964', *Report of Scrapie Seminar* (Washington: USDA): 19-40

[10] **Pattison, I. H., Gordon, W., & Millson, G. C.** (1959) 'Experimental production of scrapie in goats', *Journal of Comparative Pathology 69*: 300

and scratching.[11] Second, in the microbiology department, under David Haig, efforts to cultivate the scrapie agent using cell-culture techniques were pursued with the aim of characterising the agent more precisely.[12] Third, a team in the biochemistry department that was led by Gordon Hunter, tried a biochemical approach to its purification.[13] Fourth, one of the researchers in the functional pathology department, Richard Gibbons, collaborated with Hunter to investigate the stability of the scrapie agent.[14]

In the main, these four teams at the IRAD made little headway in their projects during the late 1950s. However, a major experimental breakthrough was made with the transmission of scrapie into small laboratory animals in 1961. Richard Chandler was testing the relative susceptibility of three strains of mice to the agent of Johnei's disease[15]. This familiarity with transmission experiments with laboratory mice, led him to suggest injecting his three strains of mice with brain material from the two types of goat scrapie. According to Michael Clarke, one of the researchers in David Haig's department:

> In the department of pathology which was headed by Ian Pattison, and Chandler was working on Johne's disease and transmission to mice, and suggested to Pattison, I think, that it might be worth trying transmission of scrapie material into mice, which was what he did. And they put the scratchy and sleepy material, which Pattison had identified, from goats into mice. And one of the two syndromes developed into disease.[16]

As we saw in the previous chapter, this success in transmission stimulated examination by other laboratories, particularly in Edinburgh. After that, researchers in both Compton and Edinburgh could initiate large-scale research projects on

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[11] **Pattison, I. H. and G. C. Millson** (1961) 'Scrapie produced experimentally in goats with special reference to the clinical syndrome', *Journal of Comparative Pathology* **71**: 101-108

[12] **Gordon, William S.** (1964) *op. cit.* note 9: 24

[13] *Ibid.*, 24.

[14] **IRAD** (1967) *op. cit.* note 6: 19-20

[15] The Johnei's (or Johne's) disease is a chronic debilitating intestinal disease of cattle. This disease was discovered by German pathologist, H. A. Johne in 1894. Johne's disease occurs in a wide variety of animals, but most often in ruminants. Ruminants are hoofed mammals that chew their cud and have a 3-4 chambered stomach. Johne's disease has been reported in all of the ruminants, but is most commonly seen in dairy cattle. It has been known to be caused by a bacterium called *Mycobacterium johnei*. (*Mycobacterium paratuberculosis)*

[16] **Clarke, Michael** (2000) Interview with author (31 May 2000: Institute of Animal Health, Compton)

scrapie in the laboratory. As Gordon Hunter acknowledged, the establishment of scrapie in laboratory animals was the first step towards doing advanced experiments. Soon after this success, Chandler and Hunter set out to show that quantitative measurements of the amounts of scrapie agent in a given amount of tissue could be made both on the basis of the length of the incubation period and by normal viral-type titration, i.e., by diluting progressively until no disease appeared after inoculation.[17] Again, as discussed in the previous chapter, this technique of titration with mice was regarded as one of major methodological advances of the early 1960s. These advances made possible further lines of research at Compton. For instance, using the mouse titration, David Haig and Michael Clarke in the microbiology department, attempted to find antibodies for scrapie, but without success.[18]

In another series of experiments, Hunter and Kimberlin found evidence that the agent might be smaller than about 30nm. This result came from the filtration experiments. Scrapie infectivity could not pass through filters with pores smaller than about 30nm in size. This implied that the active scrapie agent was roughly equivalent in size to small viral organisms like the picornaviruses.[19] However, biochemical methods failed to give any clear indication of the constitution of the agent. At the same time, Richard Chandler attempted to visualise the agent using electron microscopy.[20] According to Gordon Hunter, only fragments of smooth membranes could be identified among the main components of scrapie preparations.[21] Meanwhile, Gordon Hunter and Geoff Millson found evidence that scrapie infectivity was closely associated with molecules that form an integral part

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[17] **Hunter, G. D.** (1993) *Scrapie and mad cow disease: the smallest and most lethal living thing* (New York: Vintage Press): 64

[18] **Clarke, M. C. and D. A. Haig** (1966) 'Attempts to demonstrate neutralising antibodies in the sera of scrapie-affected animals', *The Veterinary Record* 78(19): 647-649

[19] **Hunter, G. D. and G. C. Millson** (1967) 'Attempts to release the scrapie agent from tissue debris', *Journal of Comparative Pathology* 77: 301-307; **Hunter, G. D.** (1993) *op. cit.* note *17*: 64. The *picornavirus* is among the most diverse and oldest known viruses. It was one of the first viruses to be recognised by Loeffler and Frosch 1898. The viral genome consists of a single strand of RNA with a protective coat made up of a few types of protein molecules.

[20] **Chandler, R. L.** (1967) 'Cytopathology of scrapie in the rat: an electron microscopic study of thalamic and hippocampal areas', *Research in Veterinary Science* 8(1): *98-102*

[21] **Hunter, G. D.** (1993) *op. cit.* note 17: 65

of membrane structure – a conclusion they drew from their constant failure to isolate and purify discrete particles with scrapie infectivity.[22] These findings would later be incorporated into a novel theory of scrapie put forward by the Compton researchers.

However, in the meantime, the head of the microbiology department, David Haig, was devising a new experimental plan in association with Tikvah Alper, who was in charge of a radiation unit at Hammersmith Hospital, London. This collaborative work produced an extraordinary experimental result, and became a turning point in the history of scrapie research.

3. Tikvah Alper and radiobiology

Tikvah Alper, one of the pioneers of British radiobiology, has an interesting background. She was born in South Africa, the youngest daughter of a Russian-Jewish political refugee. She majored in physics at Capetown University, and after obtaining an MA, went to Germany to research into delta rays from alpha particles under Lise Meitner, a German-Jewish woman physicist who was to play a major role in the discovery of nuclear fission.[23] Alper's paper on delta rays won the British Association Junior Medal in 1933, and according to Jack Fowler, until the 1960s her work on delta rays was still one of the few that provided evidence of cluster sizes.[24] However, Alper could not obtain her PhD in Berlin because of the growth of anti-semitic tendencies in Nazi Germany. Meitner and her work on the discovery of nuclear fission vanished from view when she had to escape from the Nazi-regime.[25] Alper, who was also Jewish, was unable to complete her research and returned to South Africa, where she married a bacteriologist, Max Stern. While she was in South Africa, she was offered the headship of the Biophysics Section of the newly

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[22] **Hunter, G.D. & Millson, G. C.** (1964) 'Further experiments on the comparative potency of tissue extracts from mice infected with scrapie', *Research in Veterinary Science* 5:149-153

[23] **Fowler, J.** (1995) 'In Memoriam: Tikvah Alper 1909-1995', *Radiation Research* **142**(1): 111

[24] *Ibid.*, 111

[25] Because of the political situation in Germany, Meitner vanished from the list of these engaged in discovering nuclear fission, and missed winning the Nobel Prize in 1945. Instead of Meitner, her collaborator Otto Hahn won the Nobel Prize [**Sime, Ruth Lewin** (1996) *Lise Meitner: A Life in Physics* (Berkeley, University of California Press)].

established National Physics Laboratory. However, she circulated a petition against Apartheid in 1951, and had to leave the laboratory and South Africa.

Alper had spent a two-year spell in Britain between 1946 and 1948. There she had encountered the Cambridge physicist, Douglas Lea, one of the leading figures in development of the target theory. The target theory was one of the important theoretical frameworks in the emerging field of radiobiology, and provided a new method of measuring the size of biological molecules.[26] It was known that enormous doses of X-rays applied to biological preparations would reduce the biological activity of those preparations. Lea showed that ionising radiation operates on a "target" basis such that a large molecule presents a correspondingly large target, and so is more likely to be hit and deactivated than a smaller molecule.[27] In other words, according to Richard Rhodes, "the more intense the bombardment (needed to deactivate a particular molecule), the smaller the molecule it would be".[28] Alper was impressed by Lea's work, and during her stay in Britain she undertook her own experiments to apply the target theory to phage. These experiments, which led her to introduce some significant qualifications into Lea's original theory, attracted a certain amount of attention at the time.[29]

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[26] **Lea, D.E.** (1955) *Action of radiations on living cells* (Cambridge: Cambridge University Press); **Casarette, Alison P.** (1968) *Radiation Biology* (Englewood Cliffs, NJ: Prentice Hall); **Alper, T.** (1979) *Cellular Radiology* (Cambridge: Cambridge Univ. Press); **Tubiana, M., Jean Dutreix, André Wambersie** (1990) *Introduction to Radiobiology* (New York: Taylor & Francis). Radiobiology or radiation biophysics has a relatively short history. Pierre Curie performed what might be considered the first radiobiological experiment when he used a radium tube to produce an ulcer on his arm, and charted its progress and ultimate healing. By the 1950s, radiobiology, especially experimental radiation biology, was gradually becoming established as a relatively independent discipline. Most researchers in radiobiology had a physics background.[26] The field has attracted engineers and physicists with a desire to contribute to medicine and biological science. Alper and Lea both belonged to this group: she was one of the most famous names in radiobiology, especially of those who came from medical physics or radiation physics [**Brown, Laurie M., Abraham Pais, Brian Pippard** (1995) *Twentieth Century Physics* (New York: American Institute of Physics press); **Hill, A. V.** (1956) 'Why biophysics?', *Science* **124** (3234): 1233-1237; **Hall, E. J.** (1993) 'Nine decades of radiobiology: Is radiation therapy any the better for it? - The Janeway Lecture 1992', *Cancer* **71**(11): 3753-3766].

[27] **Hunter, G. D.** (1993) *op. cit. note 17*: 65

[28] **Rhodes, R.** (1997) *Deadly Feast: Tracking the Secrets of a Terrifying New Plague*. (New York: Simon & Schuster): 121-122

[29] **Hornsey, S. & Denekamp, J.** (1997) 'Tikvah Alper: an indomitable spirit', *International Journal of Radiation Biology* **71**(6): 631-642: 634; According to Hornsey and Denekamp, Lea and his colleagues in Cambridge irradiated phage in dry conditions, such that only ionisations

Consequently, when Alper moved to Britain in 1951, she was able to secure a post at the MRC Experimental Radiopathology Research Unit at Hammersmith Hospital. In that unit, she conducted further research on bacteriophage, one of the most basic and simple models of a replicating life form available. Alper also came into contact with the Compton research centre through a South African born microbiologist, David Haig, who was struggling to isolate the scrapie agent by using conventional virological methods such as the ultracentrifuge. In 1961, Haig met Max Stern, who was a bacteriologist in the Wellcome laboratory, and husband of Tikvah Alper. Stern suggested at the Veterinary Research Club in London that Tikvah Alper could measure the size of the infective agent using radiation and applying target theory.[30] According to Alper, "when David Haig spoke about scrapie at a meeting of veterinary research workers, Max (Stern) suggested that the size of the scrapie agent might be found by the use of ionising radiation; and that was what started my collaboration with David [Haig] and his colleague Michael Clarke".[31] Clarke in turn recalled that '[Haig] returned from this visit full of Alper's ideas about what might be achieved – size and shape and composition of the agent.'[32]

This was a timely suggestion. Research into scrapie at Compton provided Alper with an opportunity to extend the applicability of the target theory currently being developed. Haig meanwhile was looking for other ways to tackle the problem of scrapie, owing to his repeated failure to elucidate the nature of the agent by conventional methods. Alper and Haig thus had a mutual interest in attempting to estimate the size of the agent by means of radiobiological methods. The collaborative research into scrapie looked like a potentially fruitful way of fulfilling both their interests.

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within the phage were effective. From this experiment, they obtained a single exponential survival curve, as expected from the simple target theory Lea developed. However, Alper irradiated the phage in dilute suspension, and initially found that the survival curve was sigmoid. She showed that the shape of the survival curve also depended on the time of planting the phage after irradiation, and the indirect action of the radiolysis products of water in the suspension media had an influence on the different results. This was not what Lea expected, and he was not pleased. There were some debates between Alper and Lea.

[30] *Ibid.*

[31] **Alper, T.** (1993) 'The Scrapie Enigma: Insights from Radiation Experiments', *Radiation Research* **135**: 285

[32] **Clarke, Michael** (2000) Personal communication with author (6th May 2000)

The project commenced in 1964. As it was a collaborative work, there was a division of labour between the two groups Clarke carried out the preparation of materials at Compton, Alper irradiated the samples at Hammersmith then sent them back to Compton where Haig inoculated them into mice. Each experimental process took about a year. Alper irradiated the samples using the linear accelerator (8MeV) in the Medical Research Council's Cyclotron Unit at Hammersmith Hospital, which was the first such machine dedicated to medical and biological use.[33] The aim of the experiments was simple; they intended to estimate the size of the scrapie agent; its molecular weight and diameter.[34]

4. Alper's radiobiological experiments with scrapie (1964-1969)

In this period, two series of experiments were conducted which depended upon the principles of radiobiology. The first experiment was to follow the work of Douglas Lea on the use of quantification of inactivation by ionising radiation to determine target size. In the second experiment, exposure to ultraviolet (UV) light was tried, in order to determine the degree to which the scrapie agent could withstand UV radiation. In both cases, the infectious material came from mice brain infected with "Chandler's strain" of the scrapie agent.

4.1. Estimating the size of the scrapie agent

Alper's first experiment involved applying the target theory to the scrapie agent to obtain an estimate of its size. According to the target theory, molecular size and weight can be estimated from the radiation doses needed to inactivate that molecule. The size of a biomolecule is inversely proportional to the radiation dose required to inactivate a given fraction of the population. The freeze-dried samples of scrapie-

[33] This machine was installed in 1952, and switched off for the last time in 1984. It was used for clinical and non-clinical research. As mentioned, it is the first 8 MeV-capacity accelerator and this made the scrapie research possible [**Bewley, D.K.** (1985) 'The 8MeV linear accelerator at the MRC Cyclotron Unit, Hammersmith Hospital, London', *British Journal of Radiology* **58**: 213-217].

[34] **Alper, T., D.A. Haig, et al.** (1966) 'The exceptionally small size of the scrapie agent', *Biochemical and Biophysical Research Communications* 22: 278

infected material were taken and exposed to various doses of radiation from the linear accelerator at the Hammersmith hospital. Then, Haig's team injected the samples into healthy mice to see if that material was rendered less or non-infectious, and the results were compared to what was already known about the effects of the same kind of radiation on other biological molecules and small molecular assemblages including ribonuclease and various bacteriophages.[35]

Initially, they used doses up to 2 megarads, which would normally be sufficient to inactivate the majority of infectious bacteria and viruses. However, they found that these doses had no effect on the infectivity of the scrapie material. Consequently, they exposed that material to larger doses of radiation from 2 to 25 megarads, and found that a minimum dose of around 5 megarads was needed to render that material non-infectious, i.e. to inactivate the infectious agent.[36] According to Clarke, who was participating in this project:

> In the first experiment, doses of up to 2 megarads were used; 2.5 megarads was the dose used in those days to sterilise heat labile material. No measurable loss of infectivity was detected in any of the samples. Larger doses of irradiation were then used and inactivation of infectivity obtained, a further experiment was conducted to obtain a more accurate estimate of target size.[37]

For comparative purpose, Alper and her group already had much data on a variety of molecular weights and sizes which were calculated by the target theory, e.g. ribonuclease, lysozyme, bacteriophage R17 (RNA phage), bacteriophage T_3. The minimum dose of around 5 megarads for inactivation was about the same dose as is

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[35] Bacteriophages are small viruses, consisting of a protein coat plus either DNA or RNA, that infect and replicate in bacteria. They are widely used in laboratory research into various genetic processes, since their replication (or failure to replicate) can easily be observed in bacterial cultures. Infection of a liquid suspension of bacteria with phage results in the bacteria being lysed (basically, fragmented), with the consequence that the cloudy culture turns clear. Phage preparations can also be spread onto a gel culture or 'lawn' of host bacteria, and infection can then be seen as clear spots on the cloudy plate, making it possible to count the number of phage particles in the original preparation. Inactivation experiments on bacteriophage would be carried out be exposing a sample of the phage to radiation, then adding it to a plate or suspension of host bacteria, usually *E.Coli*, to see if those bacteria become infected or not. The properties of various phages, including molecular weight and structure, are pretty well known.

[36] **Alper, T., D.A. Haig, M.C. Clarke** (1966) *op. cit.* note 34: 279

[37] **Clarke, Michael** (2000) *op. cit.* note 32

needed to inactivate bacteriophage T_3, which is one of the smallest bacteriophages. Alper and her colleagues took this as indicating that the scrapie agent was approximately the same size as phage T_3, i.e. between 1 - 2 x 10^5 daltons.[38]

4.2. Preliminary investigation with UV radiation

In view of the high resistance of the scrapie agent to ionising radiation, Alper and her colleagues also decided to try a different kind of radiobiological investigation of the properties of the agent – looking at the effects of UV radiation, which was known to be bactericidal and viricidal, on the infectivity of the scrapie agent. Alper and her collaborators exposed scrapie infected material to a range of doses of UV from a low-pressure mercury lamp, which was known as a germicidal lamp. This experiment was similar to the ionising one in that it used the same methodology of irradiation, inoculation and titration of infectivity, but it differed from the previous one in that it was not based on target theory, i.e. it was not intended to measure the size of the scrapie agent. Rather, it was just about seeing whether UV had similar effects on the scrapie agent as on other infectious materials.

However, they found more surprising results than in the previous experiment. To reduce phage T_3 to 1% of infectious activity, a dose of 10^3 ergs/mm^2 of UV radiation from a standard germicidal lamp (wavelength 245nm) would suffice. However, to effect a similar reduction in activity of scrapie material, a much larger dose of radiation of more than 2.4 x 10^4 ergs/mm^2 was required. In other words, the scrapie agent was extraordinarily resistant to deactivation by UV light.[39] The researchers themselves were confused by this extraordinary outcome. Clarke explains the situation at the time:

> When there was an assay involved, I was looking at mice every week to score. So that one can see a picture developing from fourteen or so weeks onwards up to thirty, the mice developing scrapie, and one can get a feel for a comparison between one example and another. So in the first experiment, I got a feeling early on that the irradiation that had been used was not effective, because there was no reduction compared with the controls. There are some months while the experiment is developing, when one has an

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[38] **Alper, T.** (1992a) 'New insight into the nature of scrapie from old radiation results', *British Journal of Radiology, supplement* **24**: 1

[39] **Alper, T., D.A. Haig, M.C. Clarke** (1966) *op. cit.* note 34: 281

> opportunity to think about the implications of what has actually been happening. It was Tikvah Alper who suggested, because we got no reduction with the first experiment using ionising radiation, that we should try ultraviolet light. Ultraviolet light of wavelength 245 was known to be viricidal or bactericidal. It was a common enough thing to use at that time, and so we did the experiment and we got no inactivation. [40]

How to explain these results? Germicidal UV light of the kind used in this experiment was generally understood to inhibit the infectivity of viruses and bacteria by disrupting the structure of nucleic acids. Alper and Haig suggested a possible hypothesis, that scrapie infection might not involve replication of nucleic acids. In the paper of 1966, they claimed that "the agent may be able to increase in quantity without itself containing nucleic acid".[41] As an additional argument in support of this very unorthodox proposal, they pointed to the previous experiment, which suggested that the scrapie agent had a molecular weight of 1-2 x 10^5 daltons. This is very small, and so would be in keeping with the view that the scrapie agent has a relatively simple structure which perhaps does not contain nucleic acid.

4.3. Further UV experiments

In 1967, Alper and her collaborators launched a further experiment using ultraviolet light. One aim of the experiment was to reconfirm the extraordinary characteristics of the agent that had been observed in the previous experiments. Particularly, they intended to throw more light on the question of the involvement of nucleic acid in the replication of the scrapie agent. But this time the material was exposed to two different wavelengths of UV light of 254nm and 280nm, understood to have different effects on biological molecules. In radiobiology, the wavelength of 254nm is understood to disrupt nucleic acids, while that of 280nm disrupts proteins.

The first half of this experiment looked at the effects of UV of around 254nm, and compared the effect on scrapie material with the effects on organisms that are known for their high resistance to UV light. These are coliphage "fr" (a bacteriophage) and *Micrococcus radiodurans* (a bacterium which is understood to have a very effective mechanism for repairing DNA damage due to UV light). Both

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[40] **Clarke, Michael** (2000) *op. cit.* note 16

[41] **Alper, T., D.A. Haig, M.C. Clarke** (1966) *op. cit.* note 36: 283

are rendered largely non-infectious or inactive by doses of 1-2 x 10^4 ergs/mm^2, i.e. their genome is damaged and their ability to replicate is almost entirely destroyed. Alper and her colleagues also compared the effect on the scrapie agent with genetic marker Nb_1, which was known to be somewhat more resistant to UV light.[42] By contrast, doses up to approximately 5 x 10^4 ergs/mm^2 of UV light at 254nm had no effect on the infectivity of the scrapie agent (see Figure 1). This meant that radiation that was understood to have a seriously damaging effect on nucleic acids did not affect the scrapie agent. It was, therefore, in keeping with the hypothesis that infectivity and replication of the agent do not involve nucleic acids.

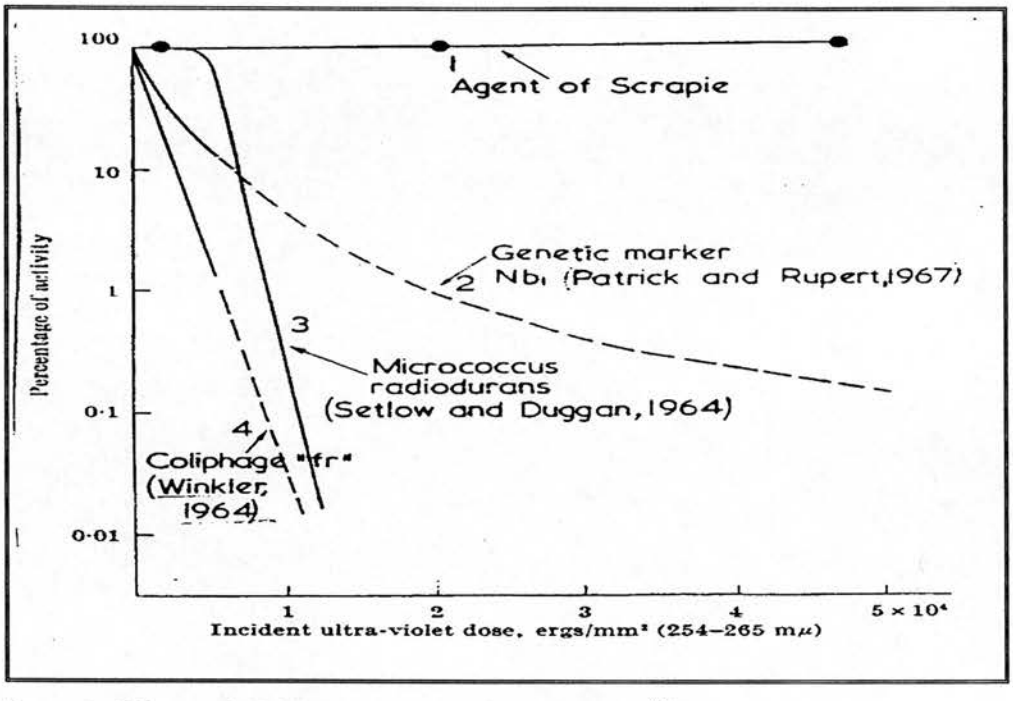

Figure1: Effects of UV light in the range 254-265mλ[43]

In the second half of this experiment, Alper and her colleagues looked also at UV light of 280 nm, which was known to deactivate proteins. If the replication of the scrapie agent was to depend on the integrity of a protein, it would be expected that

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[42] In general, genetic markers are short pieces of the genome of some organism or other that can readily be measured by titration with appropriate reagents. In the case of Nb_1, it was found that it resisted to UV treatment, and had a very effective repairing mechanism. This was reported by M. H. Patrick and C. S. Rupert in 1967. [**Patrick, M.H.& Rupert, C.S.** (1967) 'The effects of host-cell reactivation on assay of UV-irradiated Haemophilus influenza transforming DNA', *Photochemistry and Photobiology6* (1): 1-20]

[43] **Alper, T., W.A. Cramp, D.A. Haig, M.C. Clarke** (1967) *op. cit.* note1: 756

irradiation by UV light would be at its most effective at about just such a range.[44] Alper looked at the effects of doses of this light of up to 7×10^4 ergs/mm^2 on various viruses, enzymes and genetic markers, all of which were found to be severely reduced or deactivated by such light. The effect of similar doses of UV 280nm on the infectivity of the scrapie agent was not strong, but did seem to indicate a small degree of reduction in infectivity at high doses.[45] This result is shown in Figure 2, below:

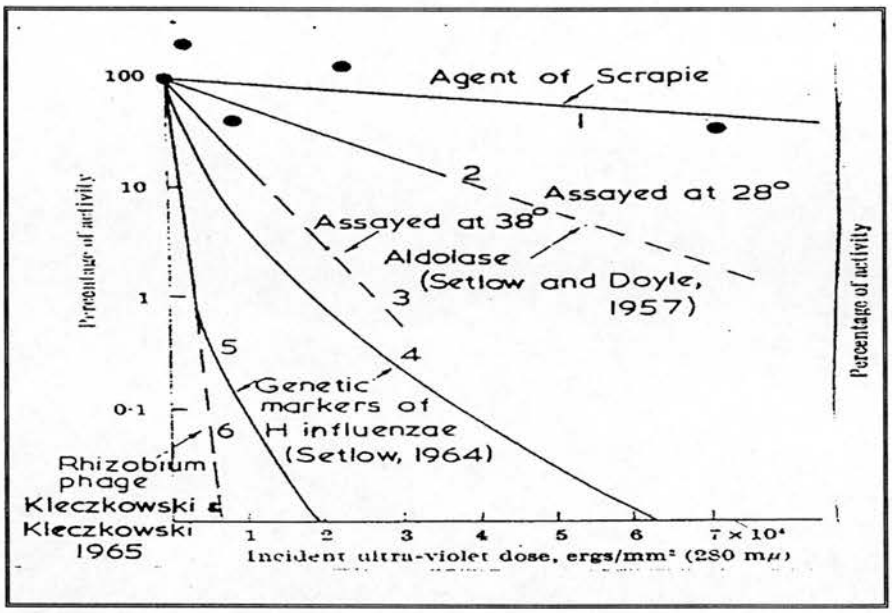

Figure 2: Effects of UV light in the range 280-285mλ[46]

Alper and her collaborators tentatively suggested that this might indicate that the scrapie agent was suffering some protein damage leading to a reduction in infectious activity. In further support of this view, they pointed out that the closest deactivation curve to that for scrapie agent was found with the enzyme aldolase, a large protein of molecular weight 1.4×10^5, i.e., pretty close to what they estimate for the scrapie agent.[47]

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[44] *Ibid.*, 765

[45] *Ibid.*, 765

[46] *Ibid.*, 766

[47] According to **Setlow, R.B. & Doyle, B.** (1957), it had highly resistant characteristics against UV light. [*Ibid.*]

In conclusion, Alper and her colleagues did not make any strong claim about what they thought that the scrapie agent was. In particular, they were careful not to say they thought it was a protein. However, they did venture the suggestion that their evidence indicated that it did not depend on a nucleic acid fraction for its replication. According to Alper, in view of "the evidence that the agent appeared effectively transparent to 'germicidal' UV, we were bold enough to suggest that the agent must be capable of replication without depending on the integrity of a nucleic acid moiety".[48]

Alper and Haig's sceptical view on nucleic acid in the agent was bucking the trend of conventional wisdom. They and their collaborative team were fully aware of the potentially explosive implication of their conclusions. Consequently, they were anxious not to appear dogmatic, and instead adopted a position of open-minded empiricism. Michael Clarke explains the situation:

> At that time I think as a group, we were open to views of others, and we tried not to establish a hypothesis. We reported what we found, and the indication from our work was that the agent might not contain nucleic acid. We didn't know what it was. We were reporting our findings, which indicated it might not be nucleic acid. What one has to take along with this, were the other factors that were known to be associated with the disease - its pathology; its lack of cellular response, no antibody response, but it is transmissible. And it appeared to be very small. What was it? We didn't know. Other people produced hypotheses of one sort or another. I think if you read our papers, we didn't actually suggest what it might be, we just suggested what it wasn't; and that it wasn't nucleic acid. But in some of the experiments that we did, I think, by implication, because we compared it with proteins, we suggested that protein might be an important component of it, other than nucleic acid.[49]

As seen in the quotation above, they claimed they were only reporting their experimental results, rather than offering speculative explanations for those results. But their willingness to accept that those results might contradict some of the most fundamental principles of biological theory – notably the "central dogma" that all life forms are coded by nucleic acid genomes – says much about their disciplinary priority. As Alper described in a letter to Haig, the work was an "essay in classical

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[48] **Alper, T.** (1993) *op. cit.* note 31: 285

[49] **Clarke, Michael** (2000) *op. cit.* note 16

radiobiology".[50] The central dogma was not highly significant for her in interpreting the experimental results; instead, she read the data on the basis of her own radiobiological principles. If radiobiological experiments failed to provide evidence of nucleic acids, Alper had no difficulty accepting that nucleic acids might not be present. This extraordinary result, and the implications Alper drew from it, initiated a controversy on the nature of scrapie that endured during the late 1960s and early 1970s.

4.4. The UV action spectrum of scrapie

In the 1960s, the only UV radiation device used in England was the 15-watt capacity germicidal lamp. Consequently, Alper and her colleagues had only been able to conduct fairly crude experiments with light of around 145 and 280nm. However, she was keen to look at the effects of more specific and intermediate wavelengths of UV light on the scrapie agent. In 1970, one of the prominent French radiobiologists, Raymond Latarjet[51] in the Institut du Radium in Paris, also known to Tikvah Alper, wrote to her saying that his colleague had developed new systems for irradiating at particular wavelengths. Collaboration between Alper and Latarjet followed on from there.

At the time, the Paris institute had a 500W high-pressure mercury lamp. This meant they could conduct experiments at various high energy levels, and more importantly, using different wavelengths of UV lights they could achieve finer control over the wavelength of the radiation generated. Alper took scrapie material over to Latarjet's laboratory, where it was exposed to UV at different wavelengths, and brought it back to Compton for inoculation research.[52]

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[50] **Clarke, Michael** (2000) *op. cit.* note 32

[51] Raymond Latarjet is regarded as one of the fathers of modern photobiology in France. He was one of the founding members of the Comite Internationale de Photobiologie in 1950, and became the president of the organisation between 1960 and 1964. He died in 1998. (**Setlow, Richard B.** (1998) "Raymond Latarjet 1911-1998" *American Society for Photobiology Newsletter 27 (4)* [online: www.photobiology.org/Newslttr/asp_nl69.html])

[52] **Clarke, Michael** (2000) *op. cit.* note 16

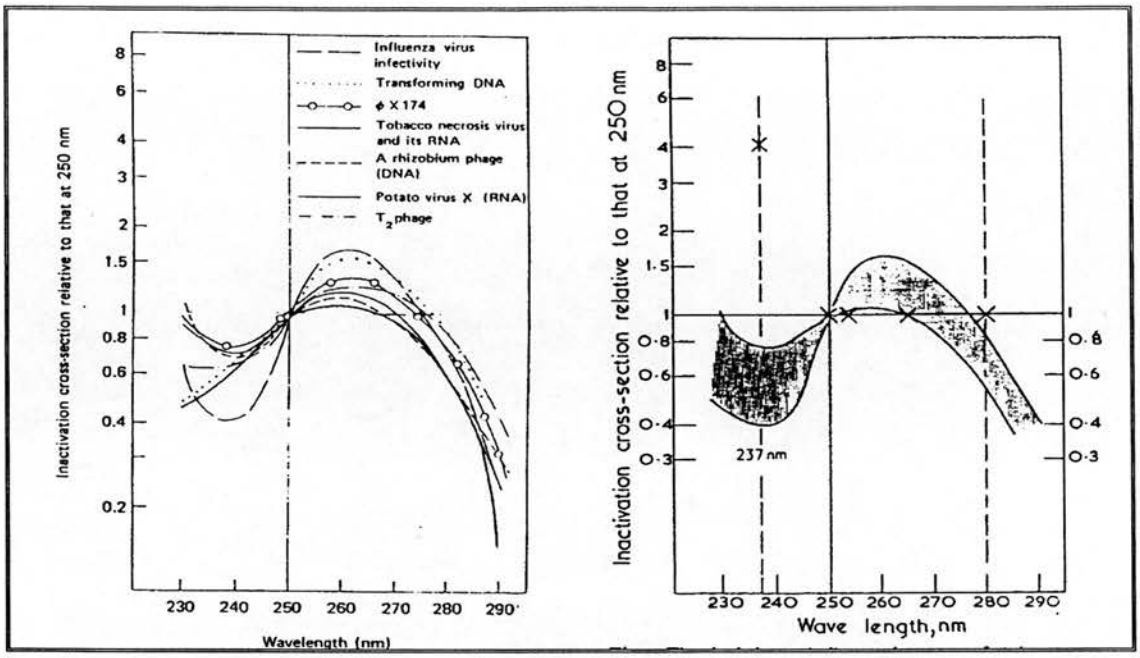

Figure 3: *Left*: action spectra for a number of viruses and virus core nucleic acids. *Right*: inactivation of scrapie agent (x) relative to the distribution of action spectra for viruses and virus core nucleic acids (shaded area).[53]

Using Latarjet's device, they exposed the material to wavelengths of 237, 254, 267, and 280nm. Alper, Latarjet and other colleagues could then compare the "action spectrum" of the scrapie agent with other known absorption spectra. Action spectra describe the extent to which ultraviolet light with different wavelengths tends to inactivate infectious organisms. In general, biological entities containing nucleic acid show a common pattern of action spectra, with a maximum inactivation with UV wavelengths of 260 to 270nm, and in the case of most viruses, a minimum in the range 235-245nm,[54] as can be seen in the shaded area in the left figure of Figure 3. The result for scrapie material was quite different with a marked increase rather than a reduction of inactivation at 237nm, and no peak at around 260-270nm.

Alper and her colleagues took this as further confirmation that the scrapie agent was radiobiologically quite dissimilar to conventional viruses. In particular, Alper concluded that it was impossible to reconcile the behaviour of the scrapie agent with the presence of nucleic acids. As Alper recalled in 1993, "these results were excellent

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[53] **Alper, T.** (1992a) 'New insight into the nature of scrapie from old radiation results', *British Journal of Radiology, supplement* **24**: 34

[54] **Latarjet, R., B. Muel, D.A. Haig, M.C. Clarke, T. Alper** (1970) 'Inactivation of the Scrapie Agent by Near Monochromatic Ultraviolet Light', *Nature* 227 (26 September, 1970): 1342

confirmation of the non-involvement of nucleic acid in scrapie replication".[55] Thus where the previous experiments led to the speculation that the scrapie agent is much smaller than most normal infectious agents, and perhaps that it contained no nucleic acid structure, after this experiment, what had been mere speculation became confident belief that scrapie agent could replicate without depending upon nucleic acid.

5. Building hypotheses to explain results: the 1967 gold rush

Whilst Alper and Haig's team reported unusual characteristics of the scrapie agent from their radiobiological experiments, some researchers rushed to produce their own versions of speculation on the nature of the agent. In this sense, 1967 was the year of the gold rush as a number of Alper's colleagues at Compton sought to explain her results.

Soon after Alper and Haig's team reported their results of radiobiological data, other researchers in the pathology department, Iain Pattison and Katherine Jones, suggested that a small protein might be responsible for transmitting the disease. They claimed to have discovered the scrapie agent from the tumours of mice, and from nucleoprotein material from normal mice. Moreover, the causal agent of the tumours (allergic encephalomyelitis), identified as a basic polypeptide, had a resemblance of the scrapie agent. From this result, Pattison and Jones speculated "if the possibility is considered that the scrapie agent is present in an inhibited form in normal tissue and in a released form in scrapie tissue, such unmasking would provide an alternative explanation to self-replication."[56] However, this bold claim was dismissed as due to laboratory contamination. According to Gordon Hunter in 1992, Pattison, like so many others, overstated his case, while cross-contamination was obviously quite inadequately controlled.[57] Later, Pattison himself described the

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[55] **Alper, T.** (1993) *op. cit.* note 31: 283-292

[56] **Pattison, I. H., Katharine M. Jones** (1968) 'Detection of the scrapie agent in tissues of normal mice and in tumours of tumour-bearing but otherwise normal mice', *Nature* 218 (6 April 1968): 102-104

[57] **Hunter, G.** (1992) 'The search for the scrapie agent', S. B. Prusiner, J. Collinge, J. Powell and B. Anderton (eds), *Prion Diseases of Humans and Animals* (London: Ellis Horwood): 27

situation, although he still believed in the validity of the experiment: "this suggestion was impartially reviewed in the *Nature-Times News Service* of April 8, 1968, but was disbelieved by almost all workers in the scrapie field, the consensus being that our results could be explained by laboratory contamination."[58]

Meanwhile, in a paper of 1967, Gibbons and Hunter pointed out that Alper's radiation experiments provided evidence that the agent should not be considered to be a virus, a nucleic acid, a protein or polysaccharide.[59] Instead, they formulated a theory that the disease occurred by the self-copying process of a membrane. The researchers inferred the significant role of the cell membrane from various chemical experiments, and from their own endeavours to isolate pure infectious particles from scrapie samples by differential centrifugation techniques. Despite fifty attempts to extract the isolated form of the agent, they found that infectivity was always associated with membrane debris.[60] They suggested that the scrapie agent could not be purified because of the tenacious attachment of cellular debris, particularly fragments of membrane, which are usually rather resistant to chemical and physical treatments, owing to protection by the lipid layers. The membrane theory could also explain other anomalous aspects of scrapie. The self-copying capacity of membranes could explain how the agent replicated in the absence of nucleic acid. Hunter and Gibbons also postulated that the membrane played a role in protecting the infective particles from immune detection, hence the lack of immune response. Furthermore, the researchers were able to produce evidence that was consistent with the membrane theory in terms of the operational size of the agent: the size was the same as the smallest membrane debris.[61]

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[58] **Pattison, Iain** (1988) 'Fifty years with scrapie: a personal reminiscence', *Veterinary Record 123*(26-27): 664. Michael Clarke also expressed the view Pattison's evidence for the protein theory was too weak to put forward a hypothesis. [**Clarke, Michael** (2000) *op. cit.* note 16]

[59] **Gibbons, R. A., G.D. Hunter** (1967) 'Nature of scrapie agent', *Nature 215* (2 Sept. 1967): 1041-1043

[60] **Hunter, G. D. and G. C. Millson** (1967) 'Attempts to release the scrapie agent from tissue debris', *Journal of Comparative Pathology* 77: 301-307

6. Radiobiological evidence in support of the membrane theory

Stimulated by this hypothesis, Alper and her collaborators launched a new radiobiological experiment in the late 1970s.[62] In radiobiology, it had long been known that cells are more sensitive to ionising radiations in the presence of oxygen than in anoxia. The role of oxygen was established by radiobiologists, and it was they who determined the "oxygen enhancement ratio" (OER) for living cells which is of the order of 3 in general. According to Latarjet, simpler systems like isolated nucleic acid are about equally sensitive in the presence and absence of oxygen in aqueous media (OER=1).[63] Interestingly, the presence of oxygen during irradiation greatly enhances the damaging effect of ionising radiation on biological membrane. This means, for instance, that a preparation of lysosomal enzymes and membrane components will lose its biological activity more readily when irradiated in the presence of O_2 than without. This was demonstrated by D.K. Watkins, who showed that that for sub-membrane system including lysosomes, the oxygen enhancement ratio was in the region of 10-20.[64]

Alper saw this a further means of investigating the properties of scrapie agent, and seeing how it compares to other infectious agents. Consequently, in 1978, she looked at the OER in a variety of bacteria, viruses transforming DNA, enzymes and lysosomes.[65] She found that in viruses, i.e., where the nucleic acid was surrounded by a protein coat, the OER was approximately 1 (OER=1) or less than 1 (OER <1).

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[61] **Kimberlin, R. H., G.C. Millson, et al.** (1971) 'Biochemical and histopathological changes in the brains of mice inoculated with scrapie by the intraperitoneal route', *Journal of Comparative Pathology* ***81***: 469-477

[62] **Alper, T., D.A. Haig, M.C. Clarke** (1978) *op. cit.* note 2

[63] **Latarjet, R.** (1979) 'Inactivation of the agents of scrapie, Creutzfeldt-Jakob disease, and kuru by radiations', S. B. Prusiner and W. J. Hadlow (eds), *Slow Transmissible Diseases in the Nervous System* (New York: Academic Press) **2:** 391

[64] **Watkins, D. K.** (1970) 'High oxygen effect for the release of enzymes from isolated mammalian lysosomes after treatment with ionizing radiation', *Advances in Biological and Medical Physics* ***13***: 289-306

[65] Alper and her colleagues presented a variety of data which showed the presence of oxygen when molecules were irradiated provided protection against damage to their functions, e.g., bacteriophage S_{13}, bacteriophage T_1, DNA of υX_{174}, transfer-RNA, *escherichia coli*, transforming DNA, Lysozyme, Ribonuclease, Lysosomes and scrapie [**Alper, T., D.A. Haig, M.C. Clarke** (1978) *op. cit.* note 2: 513].

However, in the case of the scrapie agent, as in the case of lysosome, the ratio was about 12 (OER=12).

Test system	Test of damage	OER
Bacteriophage S_{13}	Loss of infective activity	0.50
Bacteriophage T_1	Loss of infective activity	0.35
DNA of υX_{174}	Loss of infective activity	0.56
Poly-uracil	Loss of pheylalanine synthesising ability	0.74
Transfer-RNA E. coli	Loss of transfer activity	0.47
Transforming DNA	Loss of transforming activity	0.8-1.1
Lysozyme	Loss of enzyme activity	0.80
Ribonuclease	Loss of enzyme activity	0.74
α-Chymotrypsin	Loss of esterase activity	0.43
Lysosomes	Release of β-glucurocidase	10-20
Scrapie	Loss of infectivity	12

Table 1: Ratios of radiation doses [66]

Alper took this as evidence that replication of the scrapie agent involves some kind of membrane system or component. In addition, it appears that Alper had now obtained details of the UV absorption spectrum of endotoxin, which is a constituent of bacterial membrane. She noted that this was apparently similar to the UV action spectrum for scrapie agent that she and Latarjet had obtained in 1970. Alper also took this as evidence that scrapie replication involved a membrane component. Alper and her collaborators said that "this provides support for the original 'membrane hypothesis' of Gibbons and Hunter, and that this support is augmented by the apparent similarity between the absorption spectrum for endotoxin (a constituent of bacterial membrane) and the action spectrum for scrapie".[67] Overall, she took these findings as providing support for Gibbons and Hunter's membrane hypothesis.

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[66] *Ibid.*, 513

[67] *Ibid.*, 514

From the experiment in 1978, Alper and her colleagues concluded that the replication of scrapie was neither due to a nucleic acid core nor to protein, but rather involved replication of a plasma membrane. As Gibbons and Hunter claimed in 1967, "one may take advantage of our ignorance of the way membrane is synthesised to suggest that it may in fact be produced by a self-copying process not directly involving nuclear DNA, and that a foreign membrane fragment may become incorporated and later copied."[68] Alper thought Gibbons and Hunter's idea was supported by her experimental data. Furthermore, during the 1980s, many experimental results revealed the role of membranes and its mechanisms of growth and division.[69] The development of research on membranes led her conclude that healthy cell might incorporate fragments of foreign disease-carrying membrane, which would be copied. Thus, the replication process of the agent is dependent upon the growth and division of the cell membrane. From the viewpoint of their hypothesis, nucleic acid is not necessary to replicate the infectious agent. Unfortunately, the scientific community failed to pay attention to this hypothesis. This failure of recognition amongst scientists was partly because Alper and her colleagues omitted to institutionalise this approach, as I will discuss in the next chapter.

During the 1970s, the Agricultural Research Council refused to fund any more research on scrapie at Compton, and the group could not continue their collaborative projects any more. Then, in the early 1970s, Alper retired from the directorship of MRC Experimental Radiopathology Research Unit at Hammersmith. Nevertheless, Alper herself continued to focus on the radiological research on scrapie. Tikvah Alper died in 1995, and her co-workers changed to other research topics, eventually retiring from scientific practice.

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[68] **Gibbons, R. A., G.D. Hunter** (1967) *op. cit.* note 64: 1042

[69] **Palade, G.E.** (1983) 'Membrane biogenesis: an overview', *Methods Enzymology* 96: XXIX-LV

7. Summary

In this chapter I have described a series of experiments by Tikvah Alper and her colleagues at the Hammersmith Hospital and IRAD. During the 1960s, many research groups launched a variety of experimental projects aimed at understanding the mechanism of scrapie. Several research groups in IRAD in particular energetically studied the disease by using conventional biomedical methods. However, these were not successful. Conventional methods evidently did not work for investigating scrapie. In this context, David Haig and Tikvah Alper launched a new project to estimate the molecular size and weight of the agent using radiobiological methods. They found not only that the agent was very small, but also that it was resistant to UV irradiation. They concluded that reproduction of and infection by scrapie could not involve nucleic acids. This unusual property of the scrapie agent baffled researchers.

Soon after these experiments, scientists in IRAD put forward their own hypothetical explanations for the extraordinary characteristics of the agent. Alper and Haig found that their experimental results were compatible with one of the suggested hypotheses, the membrane theory, that was put forward by Hunter and Gibbons. Their theory could explain how replication might occur without involving nucleic acid, by locating the scrapie agent in a self-replicating plasma membrane. Since Alper and her colleagues reported the exceptional properties of the scrapie agent in 1967, the results started a controversy raging in the scrapie research community. Their results met with considerable criticism, because the conclusions implied deviation from the conventional wisdom of biology, the 'central dogma'. Moreover, the conclusion of their work were also at variance with what Dickinson's group at the Moredun-ABRO unit had shown, namely, strain variation of the agent. The two ideas were the subject of controversy during the 1970s, and no consensus was reached. In the next chapter, I will discuss how the controversy developed, and how each side criticised and reinterpreted the competing theories and data. In addition, I will also examine the outcome of the controversy between two theories at the end of the 1970s.

Chapter 5 – How controversy ends: Disputes on the nature of scrapie and their closure, 1967-1980

1. Introduction

In the previous chapters, I have introduced two cases of experimental projects on scrapie during the 1960s, and have shown how the researchers reached apparently contradictory conclusions on the nature of the scrapie agent. One group assumed on the basis of genetic experiments that the scrapie agent must contain an informational molecule.[1] The other group demonstrated that the agent was resistant to various UV lights, and concluded that it did not contain a nucleic acid genome.[2] Both speculations were based on carefully controlled experimental programmes. Soon after each group brought out their experimental data, relations between the two groups quickly degenerated into hostility and controversy that raged through the 1970s. However, the dispute came to an end with the extraordinary intervention of the governing body, the Agricultural Research Council (ARC), in the late seventies. On the whole, the scientific community and policy makers inclined to the more conventional conclusion of the first group. The radical interpretation of the second group faced too much antipathy and was passed over by the scientific community in the end.

In this chapter, I shall discuss the overall course of the controversy. I analyse how the scientific community reacted to the conflicting laboratory results. Moreover,

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[1] **Dickinson, A. G., Veronica M.H. Meikle, H. Fraser** (1968) 'Identification of a gene which controls the incubation period of some strains of scrapie agent in mice,' *Journal of the Comparative Pathology* **78**: 293-299; **Dickinson, A. G., Veronica M.H. Meikle** (1971) 'Host-genotype and agent effects in scrapie incubation: change in allelic interaction with different strains of agent,' *Molecular and General Genetics* **112**: 73-79; **Dickinson, A. G., G.W. Outram** (1979) 'The scrapie replication-site hypothesis and its implications for pathogenesis,' S. B. Prusiner & W. J. Hadlow (eds) *Slow Transmissible Diseases of the Nervous System* **2:** 13-31 (London: Academic Press)

[2] **Alper, T., W.A. Cramp, D.A. Haig, M.C. Clarke** (1967) 'Does the agent of scrapie replicate without nucleic acid?', *Nature* **214** (20 May, 1967): 764-766; **Alper, T.** (1972) 'The nature of the scrapie agent', *Journal of Clinical Pathology-supplement* **6**: 154-155; **Alper, T., D.A. Haig, M.C.**

I will show that the conflicting theories on scrapie were closely associated with distinctive laboratory cultures and traditions, and that the contradictory ideas were sustained by cultural elements specific to each laboratory, including directorial style, social relations within the laboratory, career structures, and so forth. Finally, I shall analyse the ending of the controversy by the intervention of the ARC. In the process of the closure of dispute, the alignment of interests amongst influential scientists and administrators played an important role in deciding between the two factions. I shall investigate how non-scientific factors played a role in building scientific consensus.

2. Scrapie research and the wider biological community

2.1. Reception of the two lines of research

As we have seen, in the 1960s and 1970s, a collaborative research group of the Moredun and Animal Breeding Research Organisation (ABRO) in Edinburgh speculated that the agent of scrapie could be a virus-like entity – a view that was consistent with their success in isolating various strains of the agent. They also argued that some extraordinary characteristics of the disease (e.g. long incubation period, absence of immune reaction, resistance to chemical treatments and so forth) could be explained by the peculiar genetic interaction between the host and the virus-like agent, which they labelled a virino.

At the same time, another group reached an incompatible conclusion that derived from radiobiological experiments. Tikvah Alper and David Haig's group in the Institute for Research on Animal Diseases (IRAD) at Compton showed that UV radiation of a wavelength that specifically damages nucleic acids does not deactivate scrapie agent. They concluded that the agent is either much different from conventional viruses, or that the agent may be able to replicate itself without containing nucleic acids. This ignited a firestorm of controversy in the small field of scrapie research. The groups behind the conflicting speculations failed to reach any agreement on the issue. Rather, the differences and conflicts were intensified and sustained during the 1970s.

Clarke (1978) 'The Scrapie Agent: Evidence Against its Dependence for Replication on

For the Edinburgh group, the phenomenon of strain variation, so important in their genetic-pathological work, seemed inexplicable in the absence of a small core of nucleic acids. On the other hand, from Alper's point of view, the radiobiological evidence against the presence of a genome seemed compelling. Both sets of results were derived from established methods, and the validity of the data was generally accepted by the scientific community. However, many scientists gradually came to favour the approach of the Edinburgh group as offering the more plausible explanation, since the virino theory was compatible with what was known of other infectious agent. Alper's non-viral membrane theory, on the other hand, provoked considerable interest but also ambivalence, because it departed so far from the central dogma of biology, i.e. the assumption that all living things contain nucleic acid genomes.

Alper's papers of 1966 and 1967 met with immediate scepticism from the wider scientific community. When Alper and Haig attempted to publish their extraordinary results, journals were initially reluctant to publish; this was why their findings first appeared in *Biochemical and Biophysical Research Communication*, where many people were probably not aware of it.[3] Moreover, the report of more detailed experimental results in *Nature* was initially turned down by the referees. According to Hornsey and Denekamp, an outraged letter to the Editor convinced him of the importance of the paper, and with the proofs couriered across London it was published two weeks later.[4] The paper in *Nature* met with considerable publicity and criticism. There was a flood of correspondence, so much so that the Hammersmith Hospital mailroom refused to deliver the mail to the MRC building, and Alper and Cramp had to collect it themselves.[5]

While the wider scientific community were generally prepared to accept the soundness and interest of Alper's radiobiological data, they were much more sceptical about the theoretical speculations she built on those results, i.e. that there is

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Intrinsic Nucleic Acid', *Journal of General Virology* **41**: 503-516

[3] **Clarke, Michael** (2000b) Interview with author (31 May 2000: Institute of Animal Health, Compton)

[4] **Hornsey, S. & Denekamp, J.** (1997) 'Tikvah Alper: an indomitable spirit', *International Journal of Radiation Biology* **71**(6): 631-642: 638

[5] *Ibid.*, 639

no nucleic acid in the scrapie agent. The scientific community attentively considered Alper's idea: scientific journals such as the *Lancet* and *Nature* printed editorials,[6] but the tone of these showed that they were cautious about accepting the idea as a whole. In *Nature*, the editorial ran as follows:

> It is worth recalling that even if the infective agent lacked nucleic acid, it is conceivable that the process of infection and of replication might be fitted into the now accepted framework of how protein synthesis in cells is regulated.[7]

Alper and Haig's speculations were also interesting enough to capture public attention.[8] The *Sunday Times* headline on the front page, along with the news of the beginning of the Cultural Revolution in China, was "Sheep give clue to mystery of life".[9] Alper's colleagues at IRAD evidently agreed with this optimistic appraisal, as their eagerness to hypothesise alternative means of replication makes clear.[10] In other words, the general mood in IRAD was enthusiastic about the radiobiological results.

Despite the media attention and local enthusiasm, however criticisms of Alper's results also mounted. A group of researchers in the MRC Research Unit in Demyelinating Diseases at Newcastle, E. J. Field and D. H. Adams, reproduced Alper and Haig's experiment in order to scrutinise its validity.[11] They reported that the result was fully confirmed. The authors claimed, however, that there were difficulties in accepting Alper's far-reaching conclusions. Adams thought that such a radical departure from conventional virus theory was not essential to explain the

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[6] **Lancet** (1967) 'The scrapie agent', *Lancet I* (30th September 1967): 705-706; **Nature** (1967) 'What is scrapie?', *Nature 214* (20th May 1967): 755

[7] **Nature** (1967) *op. cit.* note 6

[8] **Evening Standard** (1967) 'New life form is discovered', *The Evening Standard* (27 January 1967); **Oxford Mail** (1967) 'In search of the smallest killer of all', *The Oxford Mail* (27 January 1967)

[9] **Silcock, Bryan** (1967) 'Sheep give clue to mysteries of life', *The Sunday Times* (22 January 1967): 1, 4

[10] **Hunter, G. D., R.H. Kimberlin, et al.** (1968) 'Scrapie: a modified membrane hypothesis', *Journal of Theoretical Biology 20*: 355-357; **Pattison, I. H. & Jones, K.M.** (1967) 'The possible nature of the transmissible agent of scrapie', *The Veterinary Record 80*(1): 2-9; **Kimberlin, R. H. & Millson, G. C.** (1967) 'Some biochemical aspects of mouse scrapie', *Journal of Comparative Pathology 77*: 359-367

many exceptional properties of the scrapie agent, if certain assumptions were made concerning the nature of the viral coat.[12] Moreover, Field and Adams reinterpreted the same data of Alper and Haig: even if the size of the agent was exceptionally smaller than any other conventional viruses, the rejection of nucleic acids must be treated with caution. They observed that small circular DNA (0.8×10^6 molecular weight) had been demonstrated in *M. lysodeikticus*.[13] The duplication of the Alper-Haig data was successful, but they clearly showed that the data could be read in a different way.

Some other commentators also cast doubt on the validity of Alper's work, and thought her conclusions should be treated with caution. Carleton Gajdusek and Joe Gibbs, American medical researchers on kuru, a disease found in local tribes of Papua New Guinea with similar pathological characteristics, wrote, "it is the mystery which has been engendered by erroneous laboratory data and by the premature interpretation of UV inactivation results."[14] Moreover, in 1974, Gajdusek and Gibbs attacked Alper and Haig again:

> Unfortunately, some early studies of the physical properties of the scrapie virus were naïve and were received rather uncritically with the resulting, sometimes sensationalistic speculation as to its physical structure and mechanism of replication.[15]

Although Gajdusek and Gibbs cast strong doubt on the validity of Alper's work, they failed to establish what was wrong with the experiment. Their challenge was only based on disbelief of the data. This type of criticism had no influence on Alper's efforts to persuade the scientific community. At the time, many regarded her results, based as they were on standard radiobiological method, as shown, and therefore thought that refuting her experimental data was an unlikely proposition. She was regarded as one of the founding members of British radiobiology, so her authority on radiobiological knowledge seemed to be unchallengeable.

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[11] **Field, E. J., F. Farmer, et al.** (1969) 'Susceptibility of scrapie agent to ionizing radiation', *Nature* 222 (5 April, 1969): 90-91

[12] **Adams, D. H. & E. A. Caspary** (1967) 'Nature of scrapie virus', *British Medical Journal* ***iii*** (15 July): 173

[13] **Field, E. J., F. Farmer, et al.** (1969) *op. cit.* note 11: 91

[14] **Clarke, Michael** (2000a) Personal communication with author (6 May 2000)

In the meantime, when Dickinson and his team concluded that strain variation provided fundamental evidence for the fact that the agent contained a genetic informational molecule in 1968,[16] his speculations were generally well received by the scientific community. This was partly because strain variation was taken for granted as a conventional phenomenon by researchers at the time. Even Alper's group remarked that it could be acceptable. According to Clarke, strain variation "no great surprise to me at all, because after all as with most microbiological agents, there are many different strains, so it wouldn't have been very surprising."[17]

2.2. Alper loses support

For Dickinson, the bottom line was that a small informational molecule must control the basic mechanisms of scrapie infection. For Alper and Haig, on the other hand, it was unthinkable that there was a virus with such a small size and extraordinary resistance to UV light: the scrapie agent could not be a virus as far as radiobiological principle was concerned. That was the fundamental point on which they disagreed. Nevertheless, many researchers began to endorse Dickinson's conventional stance. Although many of Alper's fellow scientists agreed with her speculation, some of them were also not convinced by her conclusion that the scrapie agent contains no nucleic acid, and so tried to find other ways of explaining her results. They thought that departure from conventional viral knowledge was too premature and risky.

In the mid-1970s, some researchers put forward counter-evidence against the radiobiological data of Alper-Haig. One of Haig's colleagues in IRAD, Richard Kimberlin, attempted to measure the size of the infective molecule by using a different method from that used by Alper and Haig.[18] Kimberlin thought that the membrane structures and the agent might be separated by ultrasonic methods. The disrupted particles were passed through a variety of filters to measure their size. From this experiment, he found that the ultrasonicated and filtered membranes

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[15] *Ibid.*

[16] **Dickinson, A. G., Veronica M.H. Meikle, H. Fraser** (1968) *op. cit.* note 1

[17] **Clarke, Michael** (2000b) *op. cit.* note 3

indicated that the operational size was in excess of 5 x 10^7 daltons.[19] This was considerably larger than of Alper and Haig's estimate of 1.5 x 10^5 daltons.

Kimberlin attempted to reconcile his result with Alper's. He speculated that the scrapie activity was dependent on the integrity of a system that consists of two main components: one component was small and radiation insensitive, as Alper and Haig identified in 1967. The other was much larger, and could sustain damage by ionising radiation. Although Alper concluded that the agent was much smaller than any conventional viruses, Kimberlin suggested that the very small component that Alper and Haig identified might contain scrapie-specific information. Furthermore, he contemplated that the large component might play a role in protecting the core from heat, radiation and other chemical treatments.[20] His suggestion offered to reconcile the UV properties of scrapie with the presence of nucleic acid including the existence of protection or of repair mechanisms.[21]

Kimberlin's speculations showed that he was sympathetic to the assertion of the existence of scrapie-specific genetic information, put forward by Dickinson. In effect, he sought to reconcile Alper's non-viral view with the existence of nucleic acid. Interestingly, around the same time, as Kimberlin reached the conclusion of multi-structure of the agent, he turned his interests from the biochemical approach to the pathogenesis of scrapie. He thus moved closer towards Dickinson's framework, because Dickinson's group had identified themselves with pathogenetic research on scrapie.[22] Kimberlin became one of the strongest supporters for Dickinson's virino

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[18] **Kimberlin, R. H., G.C. Millson, et al.** (1971a) 'An experimental examination of the scrapie agent in cell membrane mixture', *Journal of Comparative Pathology* ***81***: 383-391

[19] *Ibid.*

[20] **Kimberlin, R. H.** (1976b) *Scrapie in the Mouse: a Model Slow Disease* (Durham: Meadowfield): 61

[21] *Ibid.*, 65

[22] **Fraser, H. and A. G. Dickinson** (1970) 'Pathogenesis of scrapie in the mouse: the role of the spleen', Nature **226** (2 May. 1970): 462-463; **Outram, G. W.** (1976) 'The pathogenesis of scrapie in mice', R. H. Kimberlin (ed.), *Slow Virus Diseases of Animals and Man* (Amsterdam: North-Holland Publishing Co.): 325-357; **Dickinson, A. G. & H. Fraser** (1975) 'Scrapie: pathogenesis in inbred mice: an assessment of host control and response involving many strains of agent', Meulen,V.T. & Katz, M. (eds), *Slow Virus Infections of the Central Nervous System: Investigational Approaches to Etiology and Pathogenesis - Workshop on Slow Virus Infections* (New York: Springer-Verlag):3-14. It is evident that pathogenesis is a subfield of general scrapie research, but particularly for Dickinson's group, it represents their research as a whole. When the

theory, and he would go on to join the newly established institute under Dickinson's leadership in 1981.

In addition to Kimberlin's experimental result, one of Alper's collaborators in Paris, Raymond Latarjet, revised her non-genome conclusion.[23] Latarjet duplicated and extended the radiobiological experiments that Alper and Haig had done. He reported an interesting feature of his radiobiological work: ribosomes, and relatively small nucleic acid molecules displayed a very similar UV inactivation spectrum to the scrapie agent. He thus confirmed Alper's findings of 1970, that the scrapie action spectrum did not show a peak at 267nm and a minimum at 240nm, at which all viruses and nucleic acid cores of viruses had shown greatly reduced effectiveness.[24] However, Latarjet also claimed in his new study that the spectrum of ribosomes indicated that scrapie was not the only exceptional case.

From this experiment, he revised Alper's conclusion, suggesting instead that nucleic acid was not necessarily absent from the scrapie agent, but is merely of very small size and coated with protein molecules. Latarjet remarked as follows in his paper:

> ...Before accepting [Alper's] revolutionary hypothesis, we must carefully examine whether the experimental action spectrum found for scrapie is absolutely incompatible with nucleic acid genome. One point is certain: if the genome is a nucleic acid, it must be embedded within a chemical complex in such a way that the non-nucleic acid component of the complex participates, by its absorption, in the inactivation of infectivity.[25]

Latarjet was once one of the enthusiasts for the Alper-Haig speculation, and he participated in their extended experiment with his equipment in Paris. Yet, after he revisited the Alper-Haig hypothesis, Latarjet came to a conclusion that scrapie might consist of very small nucleic acids within protein complexes.

Moredun-ABRO unit was extended as a unified research centre on scrapie and CJD in 1981, the centre been renamed as the ARC-MRC Neuropathogenesis Unit.

[23] **Latarjet, R.** (1979) 'Inactivation of the agents of scrapie, Creutzfeldt-Jakob disease, and kuru by radiations', S. B. Prusiner and W. J. Hadlow (eds), *Slow Transmissible Diseases in the Nervous System* (New York: Academic Press) **2:** 387-407

[24] **Latarjet, R., B. Muel, D.A. Haig, M.C. Clarke, T. Alper** (1970) 'Inactivation of the scrapie agent by near monochromatic ultraviolet light', *Nature* 227 (26 September, 1970): 1341-1343

[25] **Latarjet, R.** (1979) *op. cit.* note 23: 404

From the experimental results and revised speculations discussed above, during the mid-seventies, researchers' attitudes on the nature of scrapie gradually shifted towards Dickinson's idea. Furthermore, such modifications of Alper's original conclusion implied that there was also an on-going endeavour to reconcile Alper's non-viral theory with conventional ideas about infectious agents. Although the consensus gradually inclined toward the conventional interpretation, Alper and her group persisted their view that there is no nucleic acid. Kimberlin and Latarjet also conceded that there is no strong evidence that there is any nucleic acid: the experimental data of Kimberlin and Latarjet were not enough to demonstrate conclusively that there was a nucleic acid genome.

3. Institutional culture

Notwithstanding how the work of the two parties was received by the wider community, Dickinson and Alper persisted in disagreeing over the significance of their respective findings. In this context, the two parties found themselves at loggerheads in several conference meetings. According to Dickinson:

> Four or five times we discussed at public meetings. She (Alper) used to say [her work] proves that it can't be a nucleic acid. And I used to stand up and say, 'these days, they [Alper and her colleagues at Compton] either establish that we cannot be dealing with any nucleic acid, or they extend our understanding of the properties that nucleic acids can have, and they have to say that is the situation.' And she used to stand up and call me 'Phlogiston Dickinson'. [26]

The controversy between the Edinburgh and Compton groups was based on their pursuit of two distinctive experimental systems, each its own intrinsic standard of measurement, criteria of evaluation and interpretation. Each party of scientists believed that the experimental system they used was the *best* way of revealing the mechanism of scrapie disease. Thus, Dickinson's team focused on a long-term genetical and pathological project. In contrast, Alper and her colleagues only concentrated on radiobiological results. Moreover, from their different experimental perspectives, Dickinson and Alper took very different views, of the significance and

implications of the available evidence, which they interpreted as supporting divergent conclusions about the nature of the scrapie agent. Significantly, this polarisation of opinion was not a logically necessary consequence of the methods the two groups adopted or the results they produced. Kimberlin and Gajdusek, for instance, were able to take up positions that effectively reconciled Alper's and Dickinson's findings.

Consequently, we can raise a question concerning the two bodies of laboratory work: why did two conflicting beliefs persist without ever reaching any fundamental agreements? In order to explain this, we need to look not just at the different experimental approaches the two groups adopted, but also more generally at the distinct laboratory cultures within which they worked.

3.1. Institutional rivalry

In the late 1950s, both the Moredun-ABRO collaboration in Edinburgh and IRAD in Compton received 5-10 year grants from the US Department of Agriculture (USDA) under US Public Law 480.[27] In both Edinburgh and Compton, various approaches on scrapie were launched without any overall co-ordination and guidance. The work in Edinburgh and Compton overlapped. As Clarke remarks, "if you look at the literature, you would see there is some overlap with things that were going on: they were trying cell culture by MacKay at Moredun, just as we [Haig and Clarke] were at Compton. Mould at Moredun was doing biochemical studies, and we were doing biochemical studies here. And you can see that similar kinds of work were going on at both sites."[28] Concerned about lack of direction and duplication of effort, the governing body of the two research institutes, ARC, decided to set up a working party in order to oversee the whole situation of research in Edinburgh and Compton, after taking advice from the director of the Wistar Institute in America,

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[26] **Dickinson, Alan G.** (1999) Interview with author (15 September 1999: Dunbar, Scotland)

[27] **Dickinson, A. G.** (1998b) *Statement to the BSE inquiry, s74* (London: BSE Inquiry); **Pattison, Iain** (1988) 'Fifty years with scrapie: a personal reminiscence', *Veterinary Record 123*(26-27): 661-666

[28] **Clarke, Michael** (2000b) *op. cit.* note 3

Hilary Koprowski.[29] As a result of his advice, the Technical Committee on Scrapie Research (generally known as the scrapie working party) was set up in 1961 under the chairmanship of Scarisbrick from the head office of ARC.

However, the relationship between the two teams was not eased by the working party. Due to the overlapping of projects and their respective vested interests, the relationship between them became competitive. One of the researchers in Moredun, Hugh Fraser, explains the situation in his interview. He says, "the relation was competition. You might say there was almost antipathy between Scotland and Compton."[30] The competitive nature of the relationship was fired by the confrontational characters of the two directors, John Stamp and William Gordon. Gordon was once a researcher in Moredun until he moved to Compton. Both had strong personalities, and were fascinated with scrapie. In the late 1950s, they were at loggerheads. Even the working party decided to exclude the two directors from the regular meetings. They were urged to wait outside the committee room. Instead, senior scientists from both groups took their seats: David Haig, Iain Pattison, and Gordon Hunter from the Compton side; while Moredun was represented by Ian Zlotnik, virologist John Brotherson, and chemist Derek Mould.[31] The meetings only intensified the rivalry and personal dislike. In his interview, Clarke outlined the acrimonious character of the relationship between them:

> As well as rivalry, there was I think, it was fair to say, some dislike. I can remember a meeting at Compton, in which Alan Dickinson spoke, and Ian Pattison was, I think, upset with Dickinson. When Dickinson came to talk to me afterwards, I remembered feeling it necessary to apologise to Dickinson for what had occurred, and he just shrugged it off. I think there were certain feelings of dislike as well as rivalry.[32]

Dickinson also expresses a poor view of Pattison's scientific ability in his interview. He says that "he [Iain Pattison] was a very good histologist, but the

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[29] Hilary Koprowski was a medical scientist. In 1957, he became the director of the Wistar Institute, Philadelphia remaining there for 25 years. He made the research centre a leading light in the investigation of cancer and viral diseases. **Garfield, E.** (1982) 'A tribute to Hilary Koprowski: scientist, musician and friend', *Current Comment* 29 (19 July 1982): 5-10

[30] **Fraser, Hugh** (1999) Interview with author (30 June 1999: Science Studies Unit, Edinburgh)

[31] **Hunter, G. D.** (1993) *Scrapie and Mad Cow Disease: the Smallest and Most Lethal Living Thing* (New York: Vintage Press): 96

[32] **Clarke, Michael** (2000b) *op. cit.* note 3

moment he got into a laboratory and tried to do laboratory work it was, Pattison was the first person to claim that formaldehyde didn't inactivate infectivity, in a publication. But everybody knew this, of course. Wilson knew it."[33] Gordon Hunter witnessed other personality conflicts in the meeting: "[Iain Pattison's] vibrant clashes with Ian Zlotnik dominated the early meetings of the working party. Each of them considered that the other was stealing his results".[34]

There was, as Gordon Hunter remarked, obviously continuous tension and hostility between the Moredun and Compton contingents. In 1966, when Iain Pattison claimed to have purified and made progress towards the identification of the agent,[35] most members of the party attributed his results to cross-contamination.[36] The mistrust and disputes raged on, and not only caused Pattison to retire in 1973, but also brought about the closing down of the working party in 1969. The working party was officially wound up by the Joint Consultative Organisation (JCO), which was a newly established policy-making organisation at the top of the ARC. However, many witnesses agreed that it had already collapsed around 1966.[37] The result of the closing down was catastrophic: there was no guidance for co-ordination for the whole project. In fact, the working party was the only formal place to discuss and co-ordinate the work conducted in the two centres, and its collapse meant that there was no longer any official route for communicating between different sectors of the overall research programme. Meanwhile, each research group began to publish their own versions of speculations on the nature of scrapie around 1967. This indicated that the field was entering into a period of open competition. In this situation, a positive exchange of data and opinion could hardly

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[33] **Dickinson, Alan G.** (1999) *op. cit.* note 26. The relevant publication was **Pattison, I.H.** (1965) 'Resistance of the scrapie agent to formalin', *Journal of Comparative Pathology75*: 159-164

[34] **Hunter, G. D.** (1993) *op. cit.* note 31: 96; Dickinson alludes here to the experimental results of work done by David Wilson in the 1940s. As discussed in chapter 2, Wilson conducted a series of experiments and found that the agent was resistant to various biochemical treatments, including formalin. However, he did not publish the result, choosing instead to circulate them to the community.

[35] **Pattison, I. H., Katharine M. Jones** (1968b) 'Detection of the scrapie agent in tissues of normal mice and in tumours of tumour-bearing but otherwise normal mice', *Nature 217* (136): 102-104

[36] **Fraser, Hugh** (1999) *op. cit.* note 30; **Clarke, Michael** (2000) *op. cit.* note 3; **Hunter, G. D.** (1993) *op. cit.* note 31; **Dickinson, Alan G.** (1999) *op. cit.* note 26

be expected to come about. This climate of hostility, mistrust and cut-throat competition played an important role in reinforcing the entrenched opposing views on the nature of scrapie.

3.2. Laboratory culture

If rivalry and competition between the two parties played a certain role in encouraging their intransigence, we must also consider a specific point connected with the development of that rivalry, namely the strikingly distinctive cultures of the two laboratories. On the face of it, the rivalry and competitiveness between the contenders could be attributed to personal relations and the unique personalities involved. However, in this instance, the roots of the hostility that evolved go deeper than the merely personal level. The laboratory culture itself, including directorial styles, traditions, shared norms and specific research goals, helps to explain the antagonism pervading the relationship.

3.2.1. IRAD: Management by competition

IRAD was established as one of the first ARC institutes in 1937. When the scrapie research programme was set up in 1958, the institute had plenty of resources. It was one of the main ARC research institutes, with huge facilities. However, as far as scrapie was concerned, IRAD was not a specialised centre for sheep diseases. Actually, the institute was established for the purpose of studying cattle disorders and developing vaccines, e.g. *Brucella abortus* vaccine.[38] When William Gordon became the director in 1942, his managing style had a major influence on the whole laboratory culture of IRAD. As Henderson claimed, there was a definite change from the original concept of a Field Station providing animals and accommodation for the extension of others' work, to that of developing a research institute in its own right and a centre of excellence in its own subject.[39] Gordon dominated the

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[37] **Hunter, G. D.** (1993) *op. cit.* note 32: 97

[38] **Henderson, William** (1981) 'British agricultural research and the Agricultural Research Council: a personal historical account', Cooke, G.W. (ed.), *Agricultural Research 1931-1981: A history of the Agricultural Research Council* (London: Agricultural Research Council): 29

[39] *Ibid.*, 30

fundamental character of the institute. His style encouraged self-directed and autonomous research on animal diseases, especially scrapie.

For the twenty-five years of Gordon's directorship, all the on-going experimental projects in IRAD were not necessarily coherent with one another: individual researchers pursued their own interests. There were not even any formal meetings for the discussion and overall organisation of research projects. Michael Clarke summarises the situation:

> As far as I am aware, [Gordon] never had formal meetings with his senior scientific staff. They just got on, and did whatever was needed to be done. These people were appointed, and they went on and they did whatever. Occasionally, there would be visiting groups here who would look at what was going on, they would comment on it, but they did more or less as they liked.[40]

However, this style of research management did not always work well. The diversified system caused problems. Under Gordon's directorship, the relationship between researchers in the institute was not co-operative. Rather, he tended to encourage competition. Even when different researchers shared the same aim, establishing the chemical nature of scrapie, for instance, the laboratory culture led to rivalry between the researchers. Hugh Fraser witnessed the situation at IRAD:

> There were, I think, people at Compton working separately from one another, I don't think that Pattison had any relationship with Hunter, they worked quite separately. Kimberlin worked of course with Hunter and then became independent, but Pattison was very much isolated and worked separately. There was also Haig who had collaboration with Tikvah Alper's work which was at Hammersmith, and Pattison had a capacity to contaminate material, one of the biggest problems in this whole area.[41]

However, despite allowing his researchers to choose their own topics, this did not mean that they worked on entirely unconnected topics. On the contrary, the competitive atmosphere fostered by Gordon was based on a shared vaguely articulated idea of what the big problems were that awaited solution. One such problem was the physicochemical nature of the scrapie agent. This obscure goal tied the heterogeneous researchers together. Indeed, researchers who did not share their

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[40] **Clarke, Michael** (2000) *op. cit.* note 3

colleagues' views about what topics to address could find themselves subject to quite considerable pressure or exclusion by their colleagues.

Richard Kimberlin's case shows what happened if one became derailed from the common goal of research. Kimberlin started his career as a member of the biochemistry department. He carried out his project with Gordon Hunter and Geoff Millson. However, around the early 1970s, he began to develop an interest in the pathogenesis of scrapie, which was the main subject of the Edinburgh group. He was fascinated with Dickinson's work in Edinburgh, and decided to launch an independent project in Compton. However, the response from others there was discouraging. Kimberlin describes the circumstances surrounding his decision in the BSE Inquiry:

> I was very much in favour of moving to Edinburgh because it just seemed to be a logical progression of my career. [...] And partly because actually at Compton I had really split off from the mainstream of the work at Compton. The focus of the scrapie programme at Compton was always very much onto the nature of agent [...] And I moved off much more into areas of biology, pathogenesis rather than the nature of the agent. And with the change in climate which became very palpable. [...] The work I was doing was a little bit out of the mainstream, and I could see a potential threat here, so in order to continue my interests in pathogenesis it made a lot of sense to move up to Edinburgh. [42]

As we have seen, Kimberlin eventually made that move. To summarise the peculiar culture of IRAD: firstly, under William Gordon's directorship, each researcher was encouraged to pursue any subject that interested him/her. Secondly, relatively good resources were also provided for the self-directed experimental projects. Traditionally, IRAD was one of the main research centres of the ARC, so the ARC provided good experimental facilities, and USDA sponsored the scientific research on scrapie in the institute. Thirdly, the competitive ethos between researchers was prevalent at the time. Due to the lack of research direction and a tendency to pursue their own interests, scientists could conduct their scientific research without constraint, rather than research for a specific practical purpose.

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[41] **Fraser, Hugh** (1999) *op. cit.* note 30

[42] **Kimberlin, Richard** (1998) *Transcript of oral hearing: day 40, t40* (1 July, 1998: The BSE Inquiry): 28-29

Lastly, it should be noted that there was a shared goal of research: defining the biochemical nature of the scrapie agent.

3.2.2. Moredun-ABRO unit: collaborative research

The research team in Edinburgh, on the other hand, had a very different culture from IRAD. The Moredun research institute was established in 1926 for the purpose of researching mainly on sheep diseases. The institute was one of the first institutes established by the private sector in agricultural science. It was supported by a group of Scottish landowners and sheep farmers.[43] This meant that the main research priority was, to some extent, associated with practical issues: especially, researching on sheep diseases was considered as the main subject. According to William Martin, the director of Moredun since 1977, "the Animal Diseases Research Institute, now the Moredun Institute, was set up by landowners and farmers in Scotland to promote investigation into the diseases of livestock. The institute does have a diagnostic and specialist function with regard to livestock disease, which is available to farmers through veterinary surgeons, the Scottish College of Agriculture, the Veterinary Investigation Service and others. It does not function on behalf of, and is independent from, the Ministry of Agriculture and the ARC, as it was then known."[44] From this remark, we can see that the basic principle of the institute was concerned with practical issues facing the Scottish farming industry, as a non-governmental institute.

The practical interests of the institute pervaded the research into scrapie. The Moredun-ABRO unit had oriented its research towards pathogenesis of the disease: in particular, they examined how the disease replicated in the host. Whereas the Compton scientists aimed to elucidate the physicochemical nature of the agent, the Edinburgh group saw such questions as distracting from the more urgent practical question of how to tackle the disease. Kimberlin, for one identified this as a fundamental divergence between the two groups:

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[43] **Henderson, William** (1981) *op. cit.* note 38: 12

[44] **Martin, William** (1998) *Transcript of oral hearing: day 3, t3* (11 March, 1998: The BSE Inquiry): 35-36

> At least to me it was fundamental. The point is that when one is thinking from a practical standpoint about the implications of a new disease, it is extremely difficult, in fact I think it is almost impossible, to dwell too much on the areas of confusion about the nature of the agent, because on that basis you might actually make wrong scientific judgement about what type of policy measures would be appropriate [...] so I was far less concerned with all the various hypotheses about the nature of the agent. How these diseases develop, I was much more concerned with the biology of them, how they behave and the kind of scenarios that we had to assume, taking a worst case stance to do that, which was necessary to minimise the consequences of the new disease.[45]

Another characteristic of the culture of the Edinburgh group can be found in directorial style. During the 1960s and 1970s, John Stamp, a veterinary researcher, was the director of Moredun. Like William Gordon, he was fascinated with scrapie, and wanted to promote scrapie research. However, compared with Gordon, he was an opposite character. Stamp sought to co-ordinate the research in his institute. He contacted ABRO to start a collaborative project on genetical aspects of scrapie in 1955. He believed that a certain guideline for research was necessary. When he agreed to collaborate with setting up the Moredun-ABRO unit, he intended to provide a basic direction of research: genetic research in order to unmask the relationship between the host and the pathogen. Under this direction, Alan Dickinson, the leader of the unit, was promoted and encouraged to conduct long-term genetic-pathological experiments.[46]

From the unit, is establishment in the late 1950s, the researchers practised under a coherent culture of research. This was possible because the group was relatively smaller than the Compton group. As discussed, the research groups in IRAD pursued whatever they were interested in, and their research into scrapie followed a number of different lines. By contrast, the Moredun-ABRO unit had one direction: pathogenesis of the scrapie agent. According to Hugh Fraser, Dickinson's unit was run on a relatively small budget, so economy demanded that the research be tightly focussed.[47] Under such constraints it was unlikely that the pursuit of different interests in the unit would be possible. During the late 1960s, and the whole 1970s, the Edinburgh researchers carried out one consistent experimental project.

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[45] **Kimberlin, Richard** (1998) *op. cit.* note 43: 10-12

[46] **Stamp, J. T.** (1957) 'Address by Director of the Moredun Institute', *Animal Diseases Research Association: Annual Report and Accounts: 1956-1957* (Edinburgh: Moredun Institute): 18-25

In addition, under the leadership of Dickinson, the group shared all the information they needed within the group, and the relationship between researchers was co-operative. The role of each researcher was quite functionally defined in the Moredun-ABRO unit: the whole research process was devised in terms of distinct but related functions; for instance, there was a pathology section, a genetics section and an animal breeding section. The Moredun researchers did in fact manage to co-ordinate their efforts and share information effectively within a division of labour. In every respect, the Moredun-ABRO laboratory culture was quite contrary to that prevailing at IRAD. Whereas the IRAD researchers were competitive, the unit embodied a coherent and co-operative culture.

From this discussion of the Moredun-ABRO unit, several interesting points can be noted: firstly, the Moredun institute was established by the private sector, specifically, sheep farmers in the 1920s. For this reason, the research orientation was directed towards practical issues rather than pure scientific issues. Secondly, the directorial style of John Stamp was completely different from that of his counterpart, Gordon: Stamp specified what the Moredun-ABRO collaboration was to focus on, while Gordon let his researchers get on with whatever they wanted. Thirdly, the research unit under Dickinson's leadership worked in a coherent and stringent culture, partly as a result of their small budget which determined the research goal of the research team.

4. Cultural divergence and scientific disagreement

So far, I have shown that there were clear cultural differences between the two groups. Those cultural differences reinforced and sustained the personal animosities and interpretative differences between the groups. As seen, the culture at Moredun-ABRO unit was one of collaboration around a single question, namely the pathogenesis of scrapie. Thus while they approached the problem from a variety of perspectives including classic pathology and genetics, any theories of the nature of the disease that the team developed needed to be acceptable to colleagues working

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[47] **Fraser, Hugh** (1999) *op. cit.* note 30

in these various areas. Thus the nature of the Moredun collaboration means that the researchers there *de facto* took a broadly holistic biological view of the disease. By contrast, while the Compton researchers also approached the problem of scrapie from a number of perspectives including some very novel ones such as radiobiology, they did so not as collaborators but as competitors. Consequently, their perspective on scrapie tended to be relatively narrowly rooted in their own speciality and techniques.

This was a key point of divergence between the two groups, with implications for how they evaluated each other's work. Thus Dickinson was critical of Gordon's way of approaching the disease, which he considered simplistic. In his interview, Dickinson remarks that "Bill Gordon understood things only in very simple terms, and if you do that you can jump to very big conclusions, because you don't need to bother about the data."[48] He was similarly critical of Alper's conclusion that there is no nucleic acid in the agent which he attributed to an unwarranted reliance on an excessively narrow range of radiobiological methods. Dickinson likened Alper's assertion to the belief, common during the 1930s, that viruses were proteinaceous. This was a misunderstanding based upon half-truth that "put the cart before the horse by ignoring the virus's real genome."[49] In the 1930s, Wendell Stanley claimed that genetic information of the tobacco mosaic virus was not nucleic acid, but protein.[50] Dickinson argued that Alper and her colleagues made the mistake as Stanley did. He claimed that "Stanley was just the Ticky [Alper] of those days."[51] It is this broader perspective that led Dickinson and his colleagues to dismiss the Compton work as failing to take into account biological phenomena such as strain variation.

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[48] **Dickinson, Alan G.** (1999) *op. cit.* note 26

[49] **Dickinson, Alan G.** (1982) 'Scrapie: strategies, stalemates, and successes', *Lancet* (29 May 1982): 1221-1223; Actually, this article was written in order to criticise Staley Prusiner, when Prusiner suggested his proteinaceous nature of the agent in 1982. However, for criticising Alper's work, Dickinson used the same example of Wendell M. Stanley in his interview with author.

[50] **Stanley, Wendell M.** (1935) 'Isolation of a crystalline protein possessing the properties of tobacco mosaic virus', *Science 81*: 644-645

[51] **Dickinson, Alan G.** (1999) *op. cit.* note 26

Alper and her Compton colleagues, on the other hand, were less inclined to take account of broader biological considerations. They acknowledged the existence of strain variation, but did not see this as relevant to how they interpreted their own experiments. Thus according to one of Alper's colleagues, Michael Clarke: "people have shown with the experiment what Gordon had done with twenty different breeds of sheep. [...] So it was no surprise." They tended to dismiss any attempts to integrate their own physicochemical findings into a wider biological understanding of how the scrapie agent might function as excessively speculative. Instead, they concentrated on their own experiments and the immediate inference to be drawn from them, without placing them in a wider context of biological thinking. In his interview, Clarke goes on to claim that "I take the view that people can speculate as much as they like. But these are the experiments that we did, and this is how we interpreted it. You can speculate as much as you like, you can suggest it is green cheese if you like. It is very difficult to prove that it is not."[52]

Moreover, it should be noted that the highly competitive ethos at Compton actually encouraged risky claim-making. There was a strong motivation for individuals to get ahead, acquire prestige by making a big breakthrough. Consequently, novelty was to be welcomed, particularly if it brought publicly. In this respect, the fact that Alper's claim that scrapie agent does not involve nucleic acid might herald a major innovation in biological thinking was seen at Compton as very much in her favour. Thus even if other biologists were much more cautious, the Compton researchers immediately invested heavily in Alper's claims by making their own bold speculations on how nucleic-acid-free replication might occur. Again, this contrasts with the situation in Edinburgh, where collaborative efforts tended to entail a more conservative approach to novelty, and where there was a greater tendency for new findings to be integrated into existing knowledge.

Consequently, the cultural differences between the two research groups tended to consolidate the unyielding character of their relationship. Their divergent institutional cultures, including directorial style, structures of collaboration and competition, and distribution of responsibilities and rewards, supported very

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[52] **Clarke, Michael** (2000b) *op. cit.* note 3

different attitudes towards theoretical claim making, the pursuit of novelty and the need to maintain a broad biological perspective. These cultural divergences led in turn to mutual distrust and disdain between the two groups, and to a further hardening of attitudes that further reinforced their scientific disagreements.

5. Closure of the controversy: administrative intervention

If the heterogeneous culture of the two institutes had such influence on knowledge production, we can then go on to ask, how are such entrenched disagreements ever to be settled? The rivalry between the contenders was never resolved, nor did their controversial speculations show any sign of reconciliation. However, the controversy came to an end with the intervention of the Agricultural Research Council. In the 1970s, the ARC set up a special committee to solve the current problems of scrapie research. The intervention process had a dynamic impact on resolving the whole controversy. It brought about a systematic restructuring of scientific research procedure in the UK from the level of the ARC to scrapie laboratories.

5.1. Restructuring scientific research system in the UK

During the 1970s, the whole scientific research structure in Britain entered a new phase. In 1971, a Green Paper was published under the title "a framework for government research and development", which included a report by Lord Rothschild on "the organisation and management of government R & D".[53] This was the groundbreaking Rothschild report. Lord Rothschild reported that scientific research in Britain should be based on the principle that applied R & D - that is R & D with a practical application as its objective - must be done on a customer/contractor basis.[54] It was regarded as the first attempt to privatise scientific research. The report caused a huge controversy at the time, and had a great impact

[53] **Great Britain, Lord Privy Seal** (1971) *A Framework for Government Research and Development*, Cmnd 4841 (London: HMSO, 1971)

[54] Quotation from **Henderson, William** (1981) *op. cit.* note *38*: 93

on the scientific community as a whole.[55] From that time on, basic principles of government-sponsored scientific research would be revised.

For agricultural sciences, the impact of the report was also huge: it challenged the basis upon which scientists had developed British agricultural research since the establishment of the ARC in 1931. According to Timothy DeJager, by advocating greater intervention by the "users" of research, Lord Rothschild attempted to alter the principle by which science was linked to practice, consequently threatening the autonomy of scientists in their choice of problems.[56] The ARC was established on the basic principle that scientific research should produce practical benefits, but should also leave scientists free to pursue research interests without the constraints imposed by immediate economic needs and agendas set by the government. However, the Rothschild report required the ARC to revise its fundamental principles.

The main agenda of the reorganisation was to focus on centralisation of the funding system in terms of the "planning-by-committee method".[57] The ARC had already begun to more in this direction, joining with MAFF to set up a Joint Consultative Organisation (JCO), consisting of five boards (animal, arable crops & forage, horticulture, engineering & buildings and food science & technology).[58] The JCO sought to impose order on dispersed committees and working parties in order to redirect the whole system of scientific research. The master plan of setting up the JCO was suggested by Kenneth Mather. Under the five boards of the JCO, each agricultural sector had its own committees. Research on sheep was dealt with by the Sheep Committee of the animal board. This committee was chaired by John Stamp, the director of the Moredun Institute.[59]

Predictably, in this context, the organisational transformation had a major influence on the contending institutes in the controversy, especially the Council-

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[55] For more detailed studies on the impact of the Rothschild report on science, see **Williams, Roger** (1973) 'Some political aspects of the Rothschild affair', *Science Studies 3*: 34-46

[56] **DeJager, Timothy** (1993) 'Pure science and practical interests: the origins of the Agricultural Research Council, 1930-1937', *Minerva 31*(2): 129

[57] **Dickinson, A. G.** (1998b) *op. cit.* note *27*: 6

[58] **Henderson, William** (1981) *op. cit.* note *38*: 100

[59] *Ibid.*, 101

directed institute, IRAD. The IRAD was an archetypal institute of the Council. Thus, it embodied the basic principle of the Council, which ensured independence of researchers' interests, in its laboratory culture. The research style at Compton, in particular, was thus likely to be vulnerable to changes demanded by the Rothschild report, which posed a potential threat to maintaining the on-going research projects at Compton.

By contrast, the scrapie programme of the Moredun-ABRO unit was less swayed by the new regime. Although the unit was connected to the ARC-funded ABRO, it was also linked to the Moredun Institute, which was established by the private sector and was not under direct control by the Scottish Office. The independence of the institute also secured it from being controlled by the Ministry of Agriculture, Fisheries and Food (MAFF).[60] Moreover, Dickinson's team sought to tackle practical issues: for instance, during the late 1960s, there had been a health scare concerning a link between multiple sclerosis (MS) and scrapie. Consequently, the Edinburgh team received about £5,000 from the Multiple Sclerosis Society for research on linkage between MS and scrapie.[61] Thus the Edinburgh scrapie research was supported not just by the government through the ARC, but also by other potential "users" or at least interested parties, such as the ABRO and the MS Society. This would be looked on favourably in light of the Rothschild principles. The big shake up in science, in the policy and therefore in the science community itself, gradually pervaded the domain of scrapie research. The Rothschild regime could potentially have had a devastating effect on the less practical aspects of research laboratories. In particular, the IRAD group could be seen as being more vulnerable to disruption.

5.2. Experimental fiascos: credibility crisis in IRAD

The collapse of the scrapie working party in 1969 occurred in this context, and seems to have had a negative impact on policy makers at the ARC. Many were inclined to attribute the failure of the working party to disputes over Pattison's work

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[60] **Martin, William** (1998) *op. cit.* note 45: 35

[61] **Dickinson, A. G.** (1998b) *op. cit.* note 27: 10; **Wildy, Peter** (1976) *Report of the advisory committee on scrapie, ARC 196/77* (Advisory Committee on Scrapie: Agricultural Research Council): 3

at IRAD. As we have seen, Iain Pattison reported in 1968 that he had identified the scrapie agent, and that it consisted of protein particles without nucleic acids.[62] Most members of the working party, including members from IRAD, were inclined to doubt the validity of the experiment. One of the insiders of IRAD, Michael Clarke, describes the situation:

> There wasn't general agreement between Pattison, Haig, and Hunter as to the interpretation of the data. I think one would say that the small number of cases that he was working with, didn't leave people with very much confidence as to its validity. Just as with some of the other work that Pattison did at the time, deliberately contaminating material to try and show that the cases of scrapie that he was getting were not from contamination. Pattison produced evidence that he could recover the scrapie agent from the tumours of mice, and from nucleoprotein material from normal mice. So he believed at the time that the agent was present in all of these animals. [63]

Many people in the working party believed that Pattison overstated his case. They saw this claim as being not only unsubstantiated, but also believed his findings to be caused by cross-contamination of the experimental material. According to the recollection of Gordon Hunter, Pattison's colleague in IRAD:

> On the basis of experiments with an electro-osmometer, where cross-contamination was obviously quite inadequately controlled, he claimed that the scrapie agent was a basic protein. This was easily disproved in general terms, since basic proteins isolated from scrapie brain under fairly mild conditions contained no biological activity whatsoever.[64]

The disputes amongst members of the working party on the issue of cross-contamination marred the meetings, and the working party itself came to a somewhat precipitate end. It caused considerable damage to the credibility of IRAD, and overshadowed other researchers' work there. Some generalised that much of the work that issued from Compton, especially the more controversial claims,

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[62] **Pattison, I. H., Katharine M. Jones** (1968b) 'Detection of the scrapie agent in tissues of normal mice and in tumours of tumour-bearing but otherwise normal mice', *Nature 217* (136): 102-104; **Pattison, I. H. & Jones, K.M.** (1967) *op. cit.* note 10

[63] **Clarke, Michael** (2000b) *op. cit.* note 3

[64] **Hunter, G. D.** (1992) 'The search for the scrapie agent', S. B. Prusiner, J. Collinge, J. Powell and B. Anderton (eds) *Prion Diseases of Humans and Animals* (London: Ellis Horwood): 26

"probably results from frustration, or those were sensationalistic speculations".[65] Tentatively, it is plausible to suppose that these events may have contributed to the sceptical reception of Alper and Haig's work in the late 1960s.

Unfortunately, another similar event occurred in IRAD in the mid-1970s: the so-called, polyadenylated RNA story.[66] This concerned a research project to detect DNA in the scrapie agent devised by a PhD student. In the mid-seventies, this research student claimed to have discovered DNA elements in the agent by estimating and monitoring changes in the quantity of polyadenylated RNA in the scrapie affected brain sample.[67] Many people were excited by this development, and presented this result at a major international conference in 1979.[68] However, this result could never be duplicated. Many researchers tried to reproduce the result, but no one ever succeeded in doing so. Eventually, the finding was disregarded, and the student left the institute. This event showed the typical laboratory culture of IRAD: competition and the pursuit of one's own interests. Clarke summed up the situation in his interview:

> [There were two PhD students in the biochemistry department.] Robert Somerville was looking for a protein, and Chris Corp was supposed to be looking for a nucleic acid. I think that was the general sort of division of work. But every week, it was Somerville, he was up and the next week, it was Corp who was up. There was a sort of rivalry established, and in part encouraged, between the two to make progress. In the event, various bits and pieces of work were done, and small nucleic acids were, I think, found. Chris Corp came up with these changes in polyadenylated RNA, which seemed to Hunter and Kimberlin as a great breakthrough. [...] As a paper, [...] I didn't think was sufficiently advanced for it to be published. And I got David Haig to say, "no", because Corp wanted to publish this. I was already perhaps a bit concerned. I mean there were indications that something was not right with some of this work. When Corp went off to the States to show them how to do it, I think he was largely unsuccessful. Alistair Lax was appointed to extend the polyadenylated RNA story, and he was unable to do so, he could not repeat any of the work. Chris Corp was then brought back into the

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[65] **Clarke, Michael** (2000b) *op. cit.* note 3

[66] **Dickinson, A. G.** (1998b) *op. cit.* note 27; **Kimberlin, Richard** (1998) *op. cit.* note 43; **Clarke, Michael** (2000b) *op. cit.* note 3; **Hunter, G. D.** (1993) *op. cit.* note 32: 41

[67] **Corp, Chris R., Richard H. Kimberlin** (1976) 'Polyadenylated ribonucleic acid in normal and scrapie-infected mouse brain', *Biochemical Society Transactions* 4 (6) 1132-1133; Polyadenylated RNA is a class of RNA, which has a long polyadenylated chain. It includes most messenger RNAs.

[68] **Hunter, Gordon G.** (1979) 'The enigma of the scrapie agent: biochemical approaches and the involvement of membranes and nucleic acids', Prusiner, S.B. & W.J. Hadlow (eds), *Slow Transmissible Diseases of the Nervous System* 2 (New York: Academic Press): 365-386

> work to reproduce it, and at the end of the day, none of this work could be reproduced. And there was an internal inquiry about all. [Eventually,] he resigned.[69]

Unfortunately, this event had even more devastating effects, as far as the credibility of the institute was concerned. It came at a really bad time, when the whole research system of the ARC was being transformed following the new direction indicated by the Rothschild report. The work in IRAD was being scrutinised by the Joint Consultative Organisation (JCO). According to Clarke, "at one of the meetings, the results of some of the work and failure to reproduce [...] some of the work was discussed, and it was clear, I think that already support for the sort of scrapie work at Compton was coming to an end. I think that Jack Payne, he was then director, he was unhappy about it. He was glad to see it ended. So 1981, I think that the work [scrapie research] came to an end. But it was partly failure of polyadenylated RNA".[70] Gordon Hunter also recalled the devastating situation at the time:

> Shortly afterwards, I had to give the opening paper at a major slow virus meeting in Paris, and I had to make the sad announcement that work with our previous collaborator X must all be disregarded. But I was able to show how our subsequent work, involving Alistair Lax, Geoff Millson, and others, had repaired the damage. [...] But it was too late. The ARC ordered our programme to stop, and Alan Dickinson had the British field to himself at last.[71]

This series of experimental failures influenced the whole credibility of IRAD in the field. This could be one of the key elements in understanding why the exceptional results reported by Alper and Haig were gradually disregarded by scientists during the 1970s. Finally, the Council decided to close down the scrapie programme in IRAD at the end of the 1970s. The controversy on the nature of scrapie was brought to an end through institutional intervention.

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[69] **Clarke, Michael** (2000b) *op. cit.* note 3

[70] *Ibid.*

[71] **Hunter, G. D.** (1993) *op. cit.* note 31: 107

6. How controversy ends

This crisis of credibility was not the sole reason why the scrapie research at Compton was closed down. But it came at a time when scrapie research was being reorganised, and it fatally undermined any claim that Compton might have to retain some of that research. Around 1976, the JCO suggested establishing a scrapie advisory committee for the purpose of revising the whole research programme. This recommendation from the JCO was not only motivated by the fallout from Rothschild, but also by USDA concern about possible links between scrapie and CJD.[72] In addition, there was another outbreak of scrapie in Britain. In the early 1970s, the scrapie outbreak caused quite serious economic losses. It is estimated to have cost Swaledale breeders alone as much as 1.7 million pounds during the five years 1971-1975.[73]

At a meeting of the ARC, in 1977, the Council decided to set up the Scrapie Advisory Committee.[74] Peter Wildy, a pathologist at the University of Cambridge, was appointed chair of the committee. The members of the committee consisted in part of senior researchers from IRAD, ABRO and Moredun. Other members came from outside the scrapie research community: ARC, MAFF, and MRC sent their delegates to monitor the meetings.[75] One of the main agenda items of the committee was the issue of liaison with the Medical Research Council. The advisory committee agreed that a joint CJD-scrapie research programme should be established, in

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[72] The USDA (US Department of Agriculture) ban on meat from scrapie-infected and scrapie-exposed animals, and there was a growing interest in diseases of the human central nervous system which had perceived similarities with scrapie. The USDA concern was based upon observations that some chronic degenerative features of scrapie had similarities with certain neurological diseases such as Creutzfeldt-Jakob Disease (CJD) and Kuru. Although there was no evidence that scrapie caused these disorders in human beings, the fear of a possible link escalated at the time. [**ARC** (1976) *Meeting of the Council, ARC 311/76* (12 October 1976: ARC): 10; **ARC** (1976) *Research on scrapie of sheep, ARC 240/76* (12 October 1976: ARC): 1; **Anderson, Malcolm** (1998) *Statement to the BSE inquiry, s72* (London: BSE Inquiry)]

[73] **Wildy, Peter** (1977) *Report of the Advisory Committee on Scrapie, ARC 196/77* (12 October 1977: ARC): 6

[74] **ARC** (1977) *Meeting of the Council, ARC 220/17* (11 October 1977: ARC)

[75] The members were as follows: F. Brown (Animal Virus Research Institute), A. Dickinson (ABRO), D. Haig (IRAD), G. Hunter (IRAD), R. Kimberlin (IRAD), S.A. Hall (MAFF), Katherine Levy (Medical Research Council), C.A. Mims (Guy's Hospital Medical School), J. T. Stamp (Moredun), and J. Watson (MAFF).

collaboration with the Medical Research Council (MRC).[76] The committee also agreed that the best way to do this collaborative work between ARC and MRC would be by combining scrapie research from Moredun and Compton into a single institute, and extending it to include CJD. Finally, the committee agreed that the two existing programmes of scrapie research in Edinburgh and Compton should also be transferred into one location. In the proposal, Edinburgh was suggested as the main candidate location for the new centre.[77]

This proposal for consolidating the scrapie work in Edinburgh seems to have been drawn up by Dickinson and Kimberlin. This, at least, was the view of opponents such as Clarke, who complains that Dickinson and Kimberlin were able to by-pass the committee by submitting their proposals direct to the chair of the committee.[78] Certainly, there are strong reasons to think that opinion within the ARC was weighted in Dickinson and Kimberlin's favour. Dickinson's genetic and pathological orientation was in keeping with the views of prominent figures in ARC and MRC. An indication of this can be found in a document of the MRC. In the document we read that, "the [Neurosciences] Board had noted Dr. Dickinson's high reputation for research on scrapie, and they were confident he could provide the scientific leadership for a programme of research on slow agents."[79]

Dickinson's reputation was reinforced by a web of powerful connections within the agricultural and medical research communities. Firstly, one of the central figures of decision making at the top level of the ARC, Kenneth Mather, had been a director and mentor of Dickinson's PhD work in the University of Birmingham. The work of his group in the biometric genetics unit of the University of Birmingham became significantly influential for geneticists. Dickinson was one of the members of that group. During the 1970s, as a member of the Council, Mather played a role in

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[76] **Wildy, Peter** (1977) *op. cit.* note 73: 7

[77] **Wildy, Peter** (1978) *ARC & MRC laboratory for slow infections and CNS degenerative disease: proposal for a coordinated programme by the Agricultural Research Council and the Medical Research Council for basic research on slow-virus diseases and models for studying the dementias, ARC 150/78* (9 May 1978)

[78] **Clarke, Michael** (2000a) *op. cit.* note 14

[79] **MRC** (1980) *Proposal for a joint ARC/MRC Neuropathogenesis Unit, MRC 80/590* (23 November 1980: ARC): 1

making the master plan for the reorganisation of the ARC.[80] Dickinson's plan of genetic research on scrapie and CJD was compatible with the scientific orientation that Mather had pursued. Another interesting figure who had a close connection with Dickinson was John Jinks. When the scrapie advisory committee was built up, John Jinks was also a member of the Council. During the period 1967-85, he was also a member of fifteen of the visiting groups which the council sends periodically to inspect the institutes which it finances. Within the council, he was an influential figure in making policy. In 1984, Jinks became the Secretary and Deputy Chairman of the Agriculture and Food Research Council (ARC changed its name in 1981).[81] Significantly, he too had worked alongside Dickinson in Birmingham, and he was second co-author of Dickinson's first scientific paper in 1956.[82]

When the proposal of establishing a new MRC and ARC joint research programme at Edinburgh was put forward, Dickinson and Kimberlin were "given encouragement to proceed to detailed proposals by the Secretaries of both the ARC (Sir Ralph Riley) and the MRC (Sir James Gowans)."[83] In particular, Dickinson had a good working relationship with James Gowans, an immunologist who was constantly involved in the new research programme in Edinburgh.[84] In his interview Dickinson states, "Jim Gowans – I told you how much I admired him."[85] Finally, if the list of members of the Council meeting, which decided to establish the scrapie advisory committee in 1976, is checked carefully, then it may be seen that many people were sympathetic to the Moredun-ABRO unit, including John Stamp (the director of Moredun), J.B.W. King (the director of ABRO) and Kenneth Mather. On the other hand, the only delegate who had a connection to IRAD was William Henderson, the former director of IRAD between 1967 and 1972. In this context, the network of interests seemed more in favour of the Edinburgh side.

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[80] **Henderson, William** (1981) *op. cit.* note *38*: 50. He was a director of the Unit of Biometrical Genetics, the University of Birmingham, between 1950 and 1965.

[81] **Mather, Kenneth** (1988) 'John Leonard Jinks, 1929-1987', *Biographical Memoirs of Fellows of the Royal Society 34*: 342

[82] **Dickinson, A. G., J.L. Jinks** (1956) 'A generalised analysis of diallel crosses', *Genetics* ***41***: 65-78

[83] **Dickinson, A. G.** (1998b) *op. cit.* note 27: 12

[84] **Gowans, James L.** (1996) 'The lymphocyte: a disgraceful gap in medical knowledge', *Immunology today 17* (6): 288-291

More generally, from the overall decision-making process of establishment of new research centre, we can think about this process in scientific as well as political terms. Specifically, when seen from the point of view of Dickinson and Kimberlin's political backers within the ARC and MRC, there were compelling scientific reasons for favouring their proposals over any suggestion that scrapie work should continue at Compton. The kind of pathological and genetic approach that Dickinson and Kimberlin took towards scrapie was in keeping with the scientific orientation that predominated within the upper echelons of the ARC and MRC. As seen above, Dickinson's scientific position was close to Mather, Jinks and Gowans. In effect, it corresponds closely to what might be regarded as ARC orthodoxy.

By contrast, the novel radiobiological work undertaken at IRAD fell somewhat outside this orthodoxy. In addition, the fact that the IRAD work had resulted in two rather embarrassing experimental fiascos had presumably led many in the ARC to feel that they had made an unsuccessful gamble by investing in this work. Dickinson made much of this when he wrote to John Rook of the ARC, outlining the reasons why the ARC and MRC had decided to consolidate their scrapie research in Edinburgh. Among the five reasons he listed were: In a letter to John Rook of the ARC, Dickinson explained five elements of the rationale for establishing the new centre in Edinburgh:

> As you know, the major objective was achieved by late 1980 with the commitment of both Councils to the venture, and with the following elements having contributed to the decision:
> 1. Findings by Edinburgh group were highly relevant to the MRC.
> 2. A building was available in Edinburgh, which would only need straightforward modifications.
> 3. Part of the Compton group (those working mainly on pathogenesis) wanted to regroup in Edinburgh
> 4. The Compton group working on the biochemical nature of the agent had made little progress over two decades, and inspired little confidence for the future.
> 5. The latter point was reinforced by the Compton "nucleic acid" fiasco in 1979-1980, which convinced the outsiders on the Scrapie Advisory Committee to recommend starting the NPU and to set a termination date for work at Compton.[86]

[85] **Dickinson, Alan G.** (1999) *op. cit.* note 26

[86] **Dickinson, Alan** (1981) *A letter to John Rook, YB 81/9.23/1.1* (London: The BSE Inquiry)

Interestingly, in his letter, Dickinson pointed out the experimental fiasco in Compton as one of the rationales for regrouping all the scrapie research projects. This confirms the view that this event played a fatally negative role in undermining the credibility of the Compton group at that time. This also seems to have been the view of some key members of the scrapie advisory committee. Katherine Levy, a member of the MRC neuroscience board, and participant in the scrapie advisory committee as an MRC delegate, later told the BSE Inquiry, "I do know that there was work at Compton on the nature of the agent, which I think I am correct in saying had been rather spectacularly unsuccessful."[87]

This emerging consensus could explain why committee delegates from IRAD were powerless to resist the process of redirection in favour of Edinburgh, whilst Dickinson and Kimberlin put forward a new project, which could be a potential threat to the scrapie programme at Compton. As Hunter recollected, the debacle unfortunately coincided with a period of contracting budgets, and the Agricultural Research Council closed down the Compton scrapie programme.[88] Hugh Fraser comments on what other researchers thought about research at Compton:

> We consider there to have been an extraordinary waste of resources at Compton, where massive amounts of money and massive facilities have been available by the ARC to Compton with absolutely nothing to show. I think, Professor Peter Wildy, very good friend of ours in Edinburgh, professor of pathology in Cambridge who actually said that 'look Dickinson and your colleague, I think you are right, and your work has been successful.' [89]

Such were the general feelings amongst researchers including administrators from the ARC and MRC at the time.

Finally, in 1980, senior staff of the MRC, including Katherine Levy, visited Compton and Edinburgh to assess their suitability as sites for the unified research centre. The MRC made a decision that the new centre should be located at

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[87] **Levy, Katherine** (1998) *Transcript of oral hearing: day 22, t22* (1 July, 1998: The BSE Inquiry): 113

[88] **Hunter, G. D.** (1992) 'The search for the scrapie agent', S. B. Prusiner, J. Collinge, J. Powell and B. Anderton (eds) *Prion Diseases of Humans and Animals* (London: Ellis Harwood): 29

[89] **Fraser, Hugh** (1999) *op. cit.* note 30

Edinburgh.[90] Shortly afterwards, the scrapie advisory committee and the ARC committee agreed to establish the Neuropathogenesis Unit in Edinburgh. Alan Dickinson was appointed as the first director of the unit.[91] Accordingly, it was arranged in principle that the Compton facilities and researchers were to transfer into the new site. In fact, the programme in Compton was terminated, not transferred. Only two researchers from Compton, Richard Kimberlin and Sue Collis, moved to Edinburgh. What happened to other prominent scrapie researchers? The rest of the researchers, including Hunter, Haig, and Clarke, decided to remain in Compton. They had two alternatives: either changing their research project or retiring. David Haig decided to retire from his scientific practice. This meant that the whole project with Alper also officially came to an end. Gordon Hunter with his group continued their research on scrapie, but it gradually died out during the 1980s. Some researchers became involved in other research projects. Michael Clarke, for instance, participated in another research project on bovine diarrhoea virus.

The whole process of restructuring by the ARC can be seen as precipitating an institutional intervention in the controversy between Edinburgh and Compton. To sum up, the question of why the Committee selected Edinburgh, not Compton, as the place for the new centre, can be answered in terms of the dominating values and interests within key sections of the scientific community. It soon became apparent that the controversy between the two groups had arisen not just over different scientific hypotheses: inherent tensions and rivalries were exacerbated by different and incompatible laboratory cultures. The decision to close the radiobiological work on scrapie at Compton and concentrate instead on pathological and genetic work at Moredun/ABRO was in effect a decision to stick with safe science. Key policy-making bodies in the agricultural and medical science committees took the view that the IRAD style was not cost-effective and too risky, and that the IRAD teams had failed to make sufficient progress in scrapie research. By contrast, the Edinburgh research was seen to be safe, predictable, and generally in keeping with other work in the biological science.

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[90] **Dickinson, A. G.** (1998b) *op. cit.* note 27: 12

[91] **ARC** (1980) *A meeting of the Council, ARC 190a/80* (14 October 1980: ARC)

7. Conclusion

In this chapter, I have described the development and progress of the controversy between the Edinburgh and Compton groups on the nature of the scrapie agent. When Alper and her colleagues published a series of radiobiological experimental data, claiming that nucleic acids were not involved in the replication of scrapie, a controversy sprang up. As a result of the radiobiological data, many fellow researchers in Compton put forward various heretical speculations on the nature of scrapie, from self-replicating protein to membrane replication theory. However, those speculations faced criticisms from other scientists. Around the same time, the Edinburgh group of researchers put forward a somewhat more conventional line of speculation: virino theory, which offered an explanation of the peculiar behaviour of the pathogen and its interaction with the host organism. The dispute between the two groups intensified. As we have seen, the two research groups not only failed to find a common ground from which to consider their respective findings, but descended into growing antagonism, due as much to the different experimental cultures that they represented as to any inherent contradictions between their results.

In fact, the confrontation was not only centred on scientific issues, such as the nature of the agent, but was also associated with competitive/rival relations between the two research groups. This is the key thing that the difference between the highly individualised and competitive character of work at IRAD, which encouraged the researchers to make bold speculations on rather limited information, compared to the more collaborative work at Moredun-ABRO unit, which led the researchers to make more cautious speculations based on a wider range of biological considerations. It is evident that the workers in each institution feel a reciprocal contempt for their opposite members, which deepened the hostility between them.

More interestingly, the controversy, which looked as though it were heading for endless confrontation, was brought to an end with the dramatic intervention of the ARC, an *administrative* body. Combined with a big transformation of the ARC itself, the field of scrapie research was reorganised by the ARC. In this situation, the ARC

and its scrapie advisory committee underpinned the Edinburgh-centred reformation. Eventually, the research programmes at Compton were terminated. Alan Dickinson's research at Edinburgh continued to be carried out in the newly established research centre, namely, the Neuropathogenesis Unit.

The whole process of controversy and its ending provide an interesting insight into how science is practised. In this case, two cultural styles were in conflict, and escalated the intensity of the controversy between scientists. Throughout the controversy, Edinburgh succeeded in producing knowledge that conformed more closely to views held elsewhere in the scientific community. As seen, the pathological and genetic approach of Dickinson and Kimberlin was in keeping with the scientific orientation that predominated within the ARC and MRC. On the other hand, IRAD failed in satisfying the scientific criteria that the community shared at the time. In particular, the IRAD team embodied a high-risk culture of technical innovation and bold claim-making which resulted in the production of speculative and in some cases very insecure knowledge claims. Furthermore, this was at odds with the scientific orientation and preference of the upper ranks of the ARC and MRC.

Chapter 6 - Research into unconventional slow viruses in the United States, 1957-1980

1. Introduction

In the American context, research into scrapie presents a quite different picture from in Britain. Scrapie was not the main research priority for American scientists. Rather they were interested more in other neurological diseases like kuru, Transmissible Mink Encephalopathy (TME), and CJD, for which scrapie came to serve as a useful laboratory model. Scrapie was first noticed in the US in 1947. According to Hourrigan, who worked in the US department of Agriculture (USDA), the first case was reported in Michigan. It was immediately traced to imported British sheep.[1] Since scrapie was not endemic in the US, the main response by the USDA was simply to launch an eradication programme, in the expectation that future importation of the disease could be prevented or controlled. The USDA was interested in sponsoring further research into the disease, but the US did not have a strong tradition of research into the diseases of sheep and goats. Since Britain had a much stronger tradition of research on the topic, the USDA simply decided to fund work in Britain.[2] This financial support from the USDA resulted, as we have seen, in promoting scrapie research in Britain, and many researchers conducted large-scale experiments there during the 1960s.

By the mid-1970s, however, scrapie research was under way in a number of American laboratories – not so much as a subject of important in its own right, but because it was seen as a way to gain insight into a larger family of viral diseases for which it provided a useful experimental model. In this chapter, I will describe how scrapie came to be seen in this light. In particular, I will point to the convergence of

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[1] **Hourrigan, J. L.** (1965) 'The scrapie eradication program', D. C. Gajdusek, C. J. Gibbs Jr. and M. Alpers (eds) *Slow, Latent, and Temperate Virus Infections*. (Bethesda, National Institute of Health): 263. Between 1947 and 1964, scrapie was diagnosed in 138 flocks in 26 US states. However, in Britain the scale of outbreak was much larger [**Hourrigan, J.L.** (1964) 'Scrapie in the United States and the scrapie eradication program', *Report of scrapie seminar held at Washington D.C.* (27-30 January, 1964) (Washington, USDA): 340-360].

[2] **Pattison, I. H.** (1988) 'Fifty years with scrapie: a personal reminiscence', *Veterinary Record* **123**(26-27): 661-666

scientific interests around the concept of "unconventional slow viruses", and the role of scrapie in the formation and institutionalisation of that concept.

2. American pathway of research into scrapie-like diseases

The initial American interest in scrapie-like diseases derived not from scrapie itself, but from concern with human neurological diseases such as Kuru. One American researcher's contribution in particular should be focused on: Carleton Gajdusek. He was a paediatrician and virologist, who graduated from the Harvard medical school. While he was studying for his postgraduate degree in Caltech, he studied physical chemistry under Max Delbruck and Linus Pauling, the Nobel laureate chemist. From Caltech, he returned to Harvard for work in microbiology under John Enders, another Nobel laureate famous for his successful cultivation of poliomyelitis virus in the test tube in 1954. In 1951, Gajdusek moved to the National Institutes of Health (NIH) when his "over-ambitious projects and outlandish schemes" were accepted by one of the prominent NIH scientists, Joseph Smadel.[3] His project was basically the "study of child growth and development and disease patterns in primitive cultures". Between 1952 and 1954, Gajdusek was investigating rabies, plague and arbovirus in Iran, Afghanistan, Turkey; viruses in South America, New Britain, and Papua New Guinea; and epidemic haemorrhagic fever in Korea.[4] In 1955, he was invited by the Australian Nobel laureate, Macfarlane Burnet, to study influenza-virus genetics and infectious hepatitis virus in the Walter and Eliza Hall Institute of Medical Research in Melbourne.[5]

In 1957, while he was in Australia, he had a chance to visit Papua New Guinea to research into diseases of children. Here, he encountered a native tribe, called the Fore. Some of their members, Gajdusek found, were suffering from a mysterious disease called kuru. Immediately, he was fascinated with this human neurological

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[3] **Gajdusek, D. Carleton** (1976) 'Autobiography', *Nobel e-Museum, The Official Web Site of The Nobel Foundation,* (www.nobel.se/medicine/lauretes/1976/gajdusek-autobio.html)

[4] Ibid.; **Rhodes, Richard** (1997) *Deadly Feasts* (New York: Simon and Schuster): 32

[5] **Gajdusek, D. Carleton** (1981) 'Introduction', Judith Farquhar & D.C. Gajdusek (eds) *Kuru: Early letters and field-notes from the collection of D. Carleton Gajdusek* (New York: Raven Press): xxii

disease, and launched a pathological, epidemiological and virological examination of the disease. With his mentor in NIH, Smadel, he set up a new laboratory to launch a project concerning the transmission of kuru into laboratory animals, when he returned from Papua New Guinea in 1961. In 1965, he showed that the disease could be transmitted into other mammalian species like mice and chimpanzees. This showed that the disease is transmissible. Furthermore, Gajdusek and his colleagues discovered the transmission link between the local cannibalistic ritual and the fatal disease. For this discovery concerning "new mechanisms for the origin and dissemination of infectious diseases" of the local people in Papua New Guinea, Gajdusek won the Nobel Prize in Physiology and Medicine in 1976.[6]

William Hadlow, who qualified in animal and human pathology at Ohio State University, also played an important role in developing research into scrapie-like diseases in the US. He worked in a department of pathology in the University of Minnesota. In 1952, he was hired by Carl Eklund, who set up his laboratory at the Rocky Mountain Laboratory (RML), Montana. In the early days, he studied arbovirus infection. In 1958, his experience as a pathologist was noticed by the NIH, and they sent him to Britain to study scrapie for two years as a part of the new, USDA-sponsored, eradication programme. The USDA did not have anyone who had any experience with scrapie. Moreover, there was no laboratory set up to study scrapie in America. Consequently, the USDA decided to support British scrapie researchers, and send an American researcher to study the disease in Britain.

While Hadlow investigated pathological changes of scrapie-affected brains at the Institute for Research on Animal Diseases (IRAD) at Compton, he encountered the photomicrographs of kuru-affected brain in an exhibition at the Wellcome Museum of Medical Science in London. He found that the two diseases had a lot of pathological similarities. According to Jennifer Cooke on 28 June 1958, Bill Jellison, who was a colleague in the RML, visited Hadlow on his way home from a scientific meeting in Eastern Europe:

> Jellison casually mentioned to Hadlow an exhibition he had seen in London the previous day, which had included "a strange brain disease of a primitive people in

[6] **Goodfield, June** (1985) *Quest for the Killers* (Boston: Birkhauser)

> New Guinea". Intrigued, Hadlow journeyed to London, to the Wellcome Museum of Medical Science. On the first floor, Hadlow was drawn to large colour photographs that told the story of kuru. The display also showed the neurohistologic changes in the brain of kuru victims. It suddenly hit him. The kuru brains had holes in the neurones, just like those in scrapie brain.[7]

In an article he published shortly afterwards in the *Lancet*, Hadlow claimed that the pathological patterns of scrapie and kuru were strikingly similar, and that both diseases might be classified as belonging to the same family.[8] Gajdusek was alerted by this argument, and he became interested in the disease in sheep and goats as a possible model for kuru.[9]

Another American who took an early interest in scrapie was Carl Eklund. He was trained as a chemist and medical virologist. During his postdoctoral days, at the Rockefeller Institute he studied arbovirus, which can cause serious and potentially fatal inflammation of the brain (encephalitis). During the mid 1950s, he was single-handedly determined to study poliovirus in the Rocky Mountain Laboratory (RML), Montana. According to Hadlow, when his studies on the arboviruses were drawing to a close, he became fascinated by observations then being made on scrapie.[10] In 1961, he set up one of the first research laboratories into scrapie at the RML,[11] and investigated the behaviour of the scrapie agent in the host. Eklund thought that this was the first basic step towards the investigation of the disease in the USA.[12]

Interestingly, although these researchers became interested in the disease in sheep and goats, the initial priority of research was not scrapie at all. They had their own research subjects, and each came from a predominantly virological background; Gajdusek was a paediatrician and virologist; Gibbs was a virologist; Eklund was also a medical virologist; and Hadlow worked in virus research in his early career. Compared to British researchers, who were mostly recruited by agricultural research

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[7] **Cooke, Jennifer** (1998) *Cannibals, Cows, and the CJD Catastrophe* (London: Minerva): 38

[8] **Hadlow, William** (1959) 'Scrapie and kuru', *Lancet* ***ii*** (5 September 1959): 289-290

[9] **Gajdusek, D. Carleton** (1981) *op. cit.* note 5: xxvi

[10] **Hadlow, William J.** (1979) 'A memorial tribute to Carl M. Eklund', *Slow Transmissible Diseases of the Nervous System I.* Prusiner, S.B., W.J. Hadlow (eds) (New York: Acadmic Press): xvii-ix

[11] *Ibid.*

[12] **Eklund, C. M., R. C. Kennedy, et al.** (1967) 'Pathogenesis of scrapie virus infection in the mouse', *Journal of Infectious Diseases* ***117***: 15-22

institutes, American scientists came to scrapie research chiefly through an interest in the pathological similarities between scrapie and other neurological diseases such as kuru. Since William Hadlow suggested that both diseases had strikingly similar pathological features in 1959, American researchers began to consider scrapie as a useful model for explaining the nature of other mysterious neurodegenerative diseases.

Another significant factor was the theoretical contribution of an Icelandic pathologist, Bjorn Sigurdsson. He examined a local sheep disease in Iceland called "rida". Since the mid-1930s, four different chronic diseases had appeared in Icelandic sheep, namely pulmonary adenomatosis, maedi (progressive pneumonia), visna and paratuberculosis. Sigurdsson made a detailed study of these diseases, and from his observations suggested a new concept for categorising the mysterious acute diseases. Sigurdsson introduced his new concept, "slow virus", in the lecture delivered in London in March 1954.[13] This concept attracted much interest, because there were many chronic, long-incubation diseases which could not be explained by the conventional virus theory. The unconventional slow virus was as yet a largely hypothetical group of viruses, defined chiefly to accommodate the baffling characteristics of scrapie. But the inclusion of kuru in that group opened up what appeared to be a very promising direction of research into other virus diseases that infect humans (i.e. kuru) but could also be studied in animals (i.e. scrapie). This was an unexplored but very promising area for medical scientists, especially virologists. Many medical scientists in America believed that kuru and scrapie were representations of a new and special type of viral diseases. The fact that those unconventional diseases might be caused by a virus was huge boost to virology.

[13] **Sigurdsson, B.** (1954) 'Rida: a chronic encephalitis of sheep: with general remarks which develop slowly and some of their special characteristics', *The British Veterinary Journal* ***110***: 341-354

3. Slow virus research laboratories in America

3.1. Rocky Mountain Laboratory (RML), Hamilton, Montana

Since the early 1960s large-scale research on scrapie-like disease was carried out in the Rocky Mountain Laboratory at Hamilton, Montana. The laboratory was an outpost of the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH). The facility itself was established with research into the deadly tick-borne disease known as Rocky Mountain spotted fever. Around the turn of the century, many early settlers in the Montana foothills of the rugged Bitterroot Range of the Rocky Mountains were plagued with a disease known as "black measles", or "spotted fever". In order to examine this disease, Public Health and marine hospital service personnel and scientists from the Hygienic Laboratory undertook their field research in Montana. This was the origin of the RML as a Montana State laboratory in 1921.[14] Then the laboratory was purchased by the Federal government, and became a public research laboratory that was one of three specialised facilities of the Public Health Service (PHS) throughout the country.[15] During the 1920s, researchers developed a vaccine against the agent of spotted fever,[16] and the RML became a national vaccine factory. In addition to typhus and spotted fever vaccines, the facility also produced a yellow fever vaccine for the military during the Second World War.[17]

In 1937, the institute was redesigned as the Rocky Mountain Laboratory and assigned to the Division of Infectious Diseases, NIH. In 1955, the RML became a part of the National Institute of Allergy and Infectious Diseases. One of the main figures in slow virus research in America, William Hadlow, started his career in the institute in 1952. In 1958, the USDA asked him to visit the IRAD at Compton, England, to study scrapie. As mentioned, while he was staying at the Compton laboratory, he made an important claim that scrapie and human neurological disease, kuru, had

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[14] **Harden, Victoria A.** (1990) *Rocky Mountain Spotted Fever: history of a twentieth-century disease* (Baltimore. The Johns Hopkins University Press): 140

[15] **Harden, Victoria A.** (1986) *Inventing the NIH: Federal biomedical research policy, 1887-1937* (Baltimore, The Johns Hopkins University Press): 1967

[16] **NIAID** (1998) 'NIAID history', *National Institute of Allergy and Infectious Disease website* (www.niaid.nih.gov/final/history/history.htm)

many similar pathological features. When he returned to the RML, his boss Carl Eklund suggested he set up a new project of scrapie research at RML, beginning in the autumn of 1961.[18] Eklund played an important role in extending research on scrapie and its related diseases. According to Hadlow's memorial tribute:

> During the years that followed, his primary concern was always to gain a better understanding of the disease. And this required information on the temporal features of virus replication before any conclusions could be drawn about its pathogenesis.[19]

The early task of scrapie research was to establish "a more suitable assay system for the agent".[20] While Hadlow was visiting at Compton, he obtained samples of scrapie-affected sheep brains, and this sample became the first source for scrapie research in America. They also obtained mouse-adapted agents from IRAD at Compton around the same time.[21] Eklund and Hadlow could now conduct transmission experiments using the same laboratory mice (RML Swiss mice) as had been used in Eklund's studies on the arboviruses. With the Chandler's strain, they successfully transmitted the agent into their mice stock, and the quantitative studies, which Eklund considered so vital to progress in understanding scrapie, became possible.[22] By using their mouse model of scrapie, they conducted detailed studies on pathological changes in various organs (e.g. lymphocytic tissues, spleen, spinal cords and brain) and of the time taken for the agent to replicate in these various organs.[23] During the 1960s, subsequently, Eklund and Hadlow extended their methodology to other slowly progressing viral diseases of animals including TME, Aleutian disease in mink (AD), and progressive pneumonia of sheep. They thought that those viral diseases could be categorised in the same class of slow viruses.[24]

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[17] **Harden, Victoria A.** (1990) *op. cit.* note 14: 186

[18] **Hadlow, William J.** (1979) *op. cit.* note 10: xvii

[19] *Ibid.*, xviii

[20] *Ibid.*, xvii

[21] This agent was transmitted into mice by Richard Chandler in 1961, so it was called the Chandler's strain. This strain of agent played a significant role in promoting research in America. During the 1970s, the strain was the only source for every experiment.

[22] **Hadlow, William J.** (1979) *op. cit.* note 10: xvii

[23] **Eklund, C. M., R. C. Kennedy, et al.** (1967) 'Pathogenesis of scrapie virus infection in the mouse', *Journal of Infectious Diseases 117*: 15-22

[24] **Eklund, C.M., Hadlow, W.J., Kennedy, R.C. et al** (1968) 'Aleutian disease of mink: properties of the etiological agent and the host responses', *Journal of Infectious Diseases* 118 (5):

During the 1970s, the main task of the scrapie project in RML continued to focus on virological approaches, including using biochemical approaches in an attempt to characterise the putative virus. Their approach can be seen as conventional virology. According to Richard Race, who was a colleague of Eklund and Hadlow since 1970:

> we worked on scrapie pretty heavy until about 1979; most of our work involved animals and just studying the natural disease and the pathogenesis in natural hosts, for example, sheep. We had a lot of sheep and goats around here at that time. And we did a lot in trying to determine what tissues were infected, and how much agent was in those tissues by doing bioassays in mice. That was kind of the emphasis until about 1980, and then Bill Hadlow left at about that time.[25]

Around 1974, the scrapie research team at RML also launched a series of biophysical experiments in an attempt to isolate the scrapie agent. Stanley Prusiner, a young neurologist from San Francisco who will play an important part in the story, participated in this project. It was mainly based on the ultracentrifugation method in order to isolate a pure form of the agent, but it turned out to be largely fruitless work. After the death of Eklund and retirement of Hadlow, there was a lull. This period was not to last, however. In the early 1980s, scrapie research in the RML was resumed by a successor of Hadlow, Bruce Chesebro, and his colleagues such as Byron Caughey, Richard Race, and Suzzette Priola. Since then, the RML has made many valuable contributions to biochemical and virological research on scrapie.

3.2. The Laboratory of Central Nervous System Studies, NIH

As mentioned, Gajdusek's early interests were centred on kuru. He set up his project on the basis of conventional virological principles. Trained under prominent poliovirus researchers such as Enders and Smadel, he applied the basic techniques of virological research to researching the disease in Papua New Guinea. Initially, Gajdusek thought the disease must be a genetic disorder, because he had failed in

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510-523; **Eklund, C.M. & Hadlow, W.J.** (1969) 'Pathogenesis of slow viral diseases', *Journal of the American Veterinary Medical Association* 155 (12): 2094-2099; **Lopez, C., Eklund, C.M., Hadlow, W.J. et al.** (1971) 'Tissue culture studies of the virus of progressive pneumonia, a slow infectious disease of sheep', *Proceedings of the Society for Experimental Biology and Medicine* 138 (3): 1035-1040; **Eklund, C.M. & Hadlow, W.J.** (1937) 'Implications of slow viral diseases of domestic animals for human disease', *Medicine* 52 (4): 357-361

[25] **Race, Richard** (2000) Interview with author (14 August 2000: RML, Hamilton, Montana)

early attempts to transmit kuru into animals. However, his virological interest was renewed by Hadlow's argument that kuru could be the same type of disease as scrapie, with a similar long incubation period and spongiform changes in the brain.[26] From Hadlow's point of view, Gajdusek's approach to kuru was based on the wrong model. Gajdusek was testing for kuru on the assumption that it was a normal virus and an acute infection, which shows symptoms within days or weeks after exposure.[27] In a personal communication between Gajdusek and Hadlow in 6 July 1959, Hadlow pointed out that kuru could also have a long incubation period like scrapie. Gajdusek was instantly alerted to the possibility of long incubation periods, because they had only observed their test animals for a few weeks after inoculation.[28] This led him to change his view of kuru from an acute infectious disease to a slow infectious one. Gajdusek wrote about the situation as follows:

> The real question is not how we came to speculate that the disease might be infectious or that cannibalism might be involved in its spread. [...] Much more compelling for us than popular speculations about cannibalism was Dr. William Hadlow's suggestion, in 1959, that scrapie, an infectious chronic disease of sheep and goats, was clinically and pathologically quite similar to kuru; this suggestion led us to consider scrapie as a model for the kuru situation.[29]

At the same time, the USDA invited some British scrapie researchers to take part in a "scrapie tour" in 1959. Many prominent researchers like Herbert Parry, William Gordon, John Stamp and Alan Dickinson joined the tour. [30] Moreover, in 1960 the USDA held a scrapie conference in Washington. According to Vicent Zigas, one of Gajdusek's colleagues at NIH, "Carleton's most stimulating news was that he was very impressed with the scrapie conference in Washington. [...] He discussed the analogy with Kuru with Hadlow extensively, and planned the inoculation of monkeys and chimpanzees".[31]

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[26] **Hadlow, William** (1959) *op. cit.* note 8
[27] **Rampton, S., J. Stauber** (1997) *Mad cow USA* (Common Courage Press): 49
[28] **Goodfield, June** (1985) *op. cit.* note 6: 25
[29] **Gajdusek, D. Carleton** (1981) *op. cit.* note 5: xxiv
[30] **Dickinson, Alan G.** (1999) Interview with author (15 September 1999: Dunbar, Scotland)
[31] **Zigas, Vincent** (1990) *Laughing Death: the untold story of Kuru* (Clifton, NJ: Humana Press): 295

In June of 1961, Gajdusek made a trip to a laboratory in Keldur, Iceland to study the theory of slow viruses, which was suggested by Sigurdsson in 1954. Paul Paulsson, who was the director of the laboratory, showed him their work on the Icelandic form of scrapie, rida, and other slow infections of sheep. Also he visited the Moredun Institute at Edinburgh and the Compton laboratory. In this trip, Gajdusek observed that the prominent research centres in Iceland and Britain conducted transmission experiments into laboratory animals. He wrote later, "I came back with the conviction that we had to pursue urgently such inoculations and long-term observations of animals, especially primates."[32] Moreover, he obtained a pocketful of sealed test tubes of mouse-adapted scrapie inoculant from Compton.

Following the model of slow virus and scrapie sources from Compton, he persuaded Joseph Smadel to let him launch a new series of tests, potentially a long-term and expensive project, using monkeys and chimpanzees. He had already recruited an experienced London-based neuropathologist, Elizabeth Beck, to study the Kuru brain. His new project was impossible without the support of Smadel. Smadel's role in establishing the new laboratory was crucial. The author of *Deadly Feasts*, Richard Rhodes, describes Smadel's support for Gajdusek's research: "Smadel controlled important resources, and he proceeded to draw on those resources to facilitate Gajdusek's work. He solicited a grant of a thousand dollars from the National Foundation for Infantile Paralysis for his protégé...and he started lobbying medical journals to publish a first report on kuru that Gajdusek and Zigas had drafted and sent along to establish their priority in discovering the disease."[33] The laboratory for the study of slow, latent and temperate virus infections was established under the National Institutes of Neurological Disorders and Stroke (NINDS) in 1961. When Gajdusek set up scrapie research with Smadel, Smadel recruited a virologist, Joseph Gibbs Jr. While Gajdusek was working in the highlands of Papua New Guinea, Gibbs inoculated thousands of laboratory animals with scrapie, kuru and other human neurological diseases.

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[32] **Gajdusek, D. Carleton** (1981) *op. cit.* note 5: xxv

[33] **Rhodes, Richard** (1997) *op. cit.* note 4: 40

The main research aim in the early days was simple: transmission of kuru into experimental animals. In 1962, Gibbs and his colleagues ground up brains of kuru victims and injected these into a monkey, then into chimpanzees in 1963.[34] At last, Gajdusek's team successfully transmitted kuru agent into primates in 1966.[35] This meant that kuru was shown to be transmissible and infectious. His team also showed that cannibalism among the Fore could be blamed for the spread of kuru.[36] Moreover, they claimed that kuru, CJD and scrapie belonged to the same family.[37] Those experimental achievements on the so-called subacute progressive degenerative brain diseases secured Gajdusek a Nobel Prize for Medicine in 1976.[38] This event closed one era of experimental work in Gajdusek's laboratory.

Their research aim was gradually shifted to achieving a physicochemical understanding of the agent. In 1976, they attempted to purify the agent by using pressure cell disruption and zonal centrifugation.[39] While during the early days Gajdusek and his collaborators centered on the issue of understanding the general virological character of the disorders, since winning the Nobel Prize his team in NIH had expanded to examine other features of the disease. The laboratory itself was expanded and recruited some prominent researchers such as Paul Brown from Harvard Medical School, and an expert on biophysics, Robert Rohwer.

Furthermore, Gajdusek's team entered into collaboration with prominent French radiobiologist Latarjet to pursue radiobiological methods in studies of the agents not

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[34] **Goodfield, June** (1985) *op. cit.* note 6: 28

[35] **Gajdusek, D.C., Gibbs, C.J., Alpers, M.** (1966) 'Experimental transmission of a Kuru-like syndrome to chimpanzees', *Nature* 209 (25): 794-796; **Beck, E., Daniel, P.M., Alpers, M., Gajdusek, D.C., Gibbs, C.J.** (1966) 'Experimental "kuru" in chimpanzees: a pathological report', *Lancet* 2 (7472): 1056-1059

[36] **Gibbs, C.J. Jr. & Gajdusek, D.C.** (1970b) 'Kuru: pathogenesis and characterization of virus', *American Journal of Tropical Medicine & Hygiene* 19(1): 138-45; **Gajdusek, D.C.** (1971) 'Slow virus diseases of the central nervous system', *American Journal of Clinical Pathology* 56(3): 320-32

[37] **Gibbs, C.J. Jr., Gajdusek, D.C. et al.** (1968) 'Creutzfeldt-Jakob disease (spongiform encephalopathy): transmission to the chimpanzee', *Science* 161(839): 388-9; **Beck, E., Daniel, P.M., Matthews, W.B. et al.** (1969) 'Creutzfeldt-Jakob disease. The neuropathology of a transmission experiment', *Brain* 92(4): 699-716

[38] **Melnick, Joseph L.** (1976) 'The 1976 Nobel Prize for physiology or medicine', *Science* 194 (4268): 927-929

just of scrapie but also of kuru and CJD. Gajdusek estimated the size of kuru, CJD and scrapie agent by using ionising radiation. As we have seen, Alper and Haig had already done this type of experiment with the scrapie agent in the late 1960s.[40] It is interesting, therefore, that Gajdusek apparently rejected Alper and Haig's view that radiobiological results indicated that replication of the infectious agents did not involve nucleic acids. Latarjet himself had been involved in Alper's project in 1970.[41] However, Gajdusek like Latarjet concluded that the genetic information of all three viruses (Kuru, CJD and scrapie) was considerably smaller than that of any other known viruses of mammals.[42] In other words, he continued to suppose that the agent of scrapie was virus.

3.3. Institute for Basic Research in Developmental Disabilities (IBR), New York

During the 1970s, another group of scientists became interested in scrapie-like diseases. They were located in a newly established state-operated institute, called the New York State Institute for Basic Research in Developmental Disabilities (IBR). This laboratory, on the other hand, was established to examine the causes of developmental disabilities, provide laboratory and clinical service, and prepare materials for public and professional education in 1967.[43] The institute was initially operated by the Department of Mental Hygiene of the New York State. However, in 1977 the Office of Mental Retardation and Developmental Disabilities took control of the institute. When the institute was established in the late 1960s, the main research

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[39] **Siakotos, A.N., D.C. Gajdusek, et al.** (1976) 'Partial purification of the scrapie agent from mouse brain in by pressure disruption and zonal centrifugation in sucrose-sodium chloride gradients', *Virology 70* (1): 230-237

[40] **Alper, T., D.A. Haig, M.C. Clarke** (1966) 'The exceptionally small size of the scrapie agent', *Biochemical and Biophysical Research Communications* 22: 278-284; **Alper, T., W.A. Cramp, D.A. Haig, M.C. Clarke** (1967) 'Does the agent of scrapie replicate without nucleic acid?', *Nature* 214(20 May, 1967): 764-766

[41] **Latarjet, R., B. Muel, D.A. Haig, M.C. Clarke, T. Alper** (1970) 'Inactivation of the Scrapie Agent by Near Monochromatic Ultraviolet Light', *Nature* 227(26 September, 1970): 1341-1343

[42] **Gibbs, C.J. Jr., D.C. Gajdusek, R. Latarjet** (1978) 'Unusual resistance to ionising radiation of the viruses of kuru, Creutzfeldt-Jakob disease, and scrapie', *PNAS 75* (12): 6268-70

[43] **New York State Archives** (2000) 'Guide to the organization and history of state government', *New York State Archives Internet Document* (www.archives.nysed.gov/holding/guide/part4.htm): 10

area was focused upon diseases in the central nervous system such as autism, poliomyelitis, Alzheimer's disease,[44] multiple Sclerosis (MS),[45] and Batten disease.[46]

At this institute, one researcher in particular played a role in establishing the new project on research into scrapie-like disease. Richard Carp is a veterinarian and virologist from the University of Pennsylvania. In 1968, he set up his laboratory in the IBR in order to examine general diseases of the central nervous system (CNS). Before he came to the institute, he was dealing with the poliovirus. At the time, he encountered scrapie as a neurological disorder, and he realised that it offered a good opportunity to pursue another line of experimental research into an infectious neurological condition. In other words, his fascination in scrapie was a part of his broad interests in infections diseases of the CNS. He explains this in his interview:

> It just seemed like a very interesting area to investigate when I was starting out. I worked originally on polio, which is a very quick virus, and then I worked on Simian virus 40 for a while which is another virus that you can assay reasonably quickly - about 12 or 14 days. And I thought this was quite a challenge because here we had something that took many months to assess. And it was very interesting, and also [...] I had come to an institute that was really geared toward central nervous system disorders, so it seemed to me one of the more interesting of the CNS diseases.[47]

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[44] Alzheimer's disease is a progressive, neurodegenerative disease characterized by loss of function and death of nerve cells in several areas of the brain, leading to loss of mental functions such as memory and learning. Alzheimer's disease is the most common cause of dementia.

[45] Although multiple sclerosis (MS) was first diagnosed in 1849, the earliest known description of a person with possible MS dates from fourteenth-century Holland. An unpredictable disease of the central nervous system, MS can range from relatively benign to somewhat disabling to devastating as communication between the brain and other parts of the body is disrupted. The name "multiple sclerosis" signifies both the number (multiple) and condition (sclerosis, from the Greek term for scarring or hardening) of the *demyelinated* areas in the central nervous system.
It is believed that, currently, there are approximately 250,000 to 350,000 people in the United States with MS diagnosed by a physician. (**NINDS** (2000) 'Multiple sclerosis: hope through research', *National Institute of Neurological Disorders and Stroke website* (www.ninds.nih.gov/health_and_medical/pubs/multiple_sclerosis.htm))

[46] Batten disease is a fatal, inherited disorder of the nervous system that begins in childhood. In some cases, the early signs are subtle, taking the form of personality and behavior changes, slow learning, clumsiness, or stumbling. There is no specific method of treatment.

[47] **Carp, Richard** (2000) Interview with author (27 July 2000: the Institute of Basic Research, New York)

Around the late 1960s, Carp found that British scientists were conducting large-scale projects on scrapie, and he began to correspond with Hugh Fraser, who was a prominent scrapie researcher in Edinburgh. In 1971, Carp made a trip to Britain to visit scrapie research centres. The main aim of the trip was to look into the trends of scrapie research in the United Kingdom. During the trip he became very interested in the research methods and style of the Edinburgh group. He was most interested in genetic aspects of scrapie, and the Edinburgh group of scientists provided valuable data and methodology for research. According to him:

> It's not just the trip that is involved in this, I also read the papers and the work that the Edinburgh group did seemed to me to correspond to the standpoint that I guess I had. My interest in polio had originally been in genetic aspects of the disease, not the virus. And so I guess I was most interested in the genetic aspects of scrapie. And that was certainly being carried forward very expertly by the Edinburgh group.[48]

Since then the IBR and the Edinburgh group have maintained strong collaborative ties in their research. The Edinburgh group has provided basic ideas and experimental materials to the IBR. The IBR group needed a model for the principles and methods to pursue in their newly established project. In return, the IBR have exchanged experimental data and group members. This made for a strong alliance between the Edinburgh and American group.

The scrapie research group in the IBR during the early 1970s was not particularly productive, whereas Gajdusek's and the RML produced much experimental data. Carp and his colleagues tried to find scrapie-related effects on the behavior of blood cells. They produced evidence to show that in the case of scrapie-infected mice, the level of the white blood cells known as polymorphs was lowered.[49] However, according to Gordon Hunter, it became obvious that the results were not reproducible.[50] As Hunter remarked, the seventies was a period of false trails,

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[48] *Ibid.*

[49] **Licursi, P.C., P.A. Merz, G.S. Merz, R.I. Carp** (1972) 'Scrapie-induced changes in percentage of polymorphornuclear neutrophils in mouse peripheral blood', *Infection and Immunity6*: 370-376

[50] **Hunter, G. D.** (1992) 'The search for the scrapie agent 1961-1981', S. B. Prusiner, J. Collinge, J. Powell and B. Anderton (eds) *Prion Diseases of Humans and Animals* (New York, Ellis Horwood) : 27.

because many scientists conducted various experiments and sometimes they published premature data without sufficient repetition.[51]

Despite the frustration of such false dawns, the group in Staten Island introduced distinctive projects which were different from other scrapie research centres in the US. Like the Edinburgh group, Richard Carp thought that elucidating the relationship between the host (genetic factor) and exogenous factor (viral component) was more important than the physico-chemical nature of the agent, which was the main focus of interest during the 1970s in the US. Where Carp's project differs from the Edinburgh project was in adding some conventional virological research methods. For instance, exposure of PAM cells, a spontaneously transformed mouse cell line, to brain homogenates from mice infected with scrapie caused a relative decrease in total cell yield. Carp believed that scrapie caused the reduction of cell division.[52] This type of approach integrated the scrapie research into a broader programme of research into disease of the CNS in general. During the 1970s, Carp and his team at the IRAD were also pursuing virological research into multiple sclerosis.[53] In other words, the research project into scrapie was a part of a bigger project of studying other neurological disorders. However, the whole research orientation changed when one of his laboratory staff, who specialised in electron-microscopy, Pat Merz, discovered the first visualised form of the what was believed to be the infectious particle, famously known as "*S*crapie-*A*ssociated *F*ibrils (SAFs)".[54] Since then, research on scrapie became their main priority of research.

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[51] *Ibid.*, 27-29

[52] **Carp, R.I., Merz, G.S., Licursi, P.C.** (1976) 'Scrapie in vitro: agent replication and reduced cell yield', *Infection & Immunity* 14(1): 163-167

[53] **Carp, R.I., Licursi, P.C., Merz, G.S.** (1975) 'Multiple sclerosis-induced reduction in the yield of a mouse cell line', *Infection & Immunity* 11(4): 737-41; **Carp, R.I., Merz, G.S., Licursi, P.C.** (1976b) 'A small virus-like agent found in association with multiple sclerosis material', *Neurology* 26 (6 PT 2): 70-1; **Carp, R.I., Warner, H.B., Merz, G.S.** (1978) 'Viral etiology of multiple sclerosis', *Progress in Medical Virology* 24: 158-77

[54] **Merz, P.A., R.A. Somerville, et al.** (1981) 'Abnormal fabrils from scrapie-infected brain', *Acta Neuropathologica 54* (1): 63-74. This finding was regarded as one of the major breakthroughs in this field. I will discuss this issue later

3.4. Department of Veterinary Science, University of Wisconsin, Madison

Veterinary research at the University of Wisconsin, Madison has long been strongly associated with local farming interests. As with other research schools in the US, the Madison research group did not initially focus on scrapie, but on another disease in mink called Transmissible Mink Encephalopathy (TME). As is becoming clear, scrapie research in America shows a different developmental pathway from Britain: the majority of scrapie researchers came on board as an extension of other research interests, e.g. virological, or medical interests, whereas British research on scrapie derived from agricultural demands. In the Madison, however, local agricultural interests played an important role in promotion of the research. The state of Wisconsin has a nickname, "the dairy state". Also the University of Wisconsin, Madison (UW-Madison) has provided many valuable resources for local farmers, and developed revolutionary techniques of pest management, fertilizer application, irrigation, crop rotation, animal insemination and disease control.[55] This means that the agricultural industry were able to influence academic research. Following such strong demands from the agricultural sector, UW-Madison specialised particularly in bovine-related research.

Alongside the strong tradition of research on bovine diseases, some members of the department were also interested in diseases in mink. In fact, the United States accounted for about a third of the world's total mink production, and Wisconsin is the largest producer of commercially-raised mink pelts in the country.[56] Consequently, it is not surprising that the department has a strong tradition of research into mink-related diseases. One of the mink diseases was TME. It was thought that the disease was caused by a virus-like agent that produces a spongiform-like change in brain.[57] TME is a rare disease, but caused enormous economic losses in the commercial mink industry. According to Rampton and Stauber, in 1961 the disease struck five ranches in Wisconsin, killing between 10% to

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[55] **Rampton, S., J. Stauber** (1997) *op. cit.* note 27: 86

[56] *Ibid.*, 86

[57] **Marsh, R.F. & Hanson, R.P.** (1969) 'Physical and chemical properties of the transmissible mink encephalopathy agent', *Journal of Virology* 3(2): 176-80, 1969

30% of the animals on each ranch. Other incidents occurred in 1963 in Idaho, in Canada and Wisconsin.[58]

Robert Hanson and Richard Marsh were the central figures of research on TME. Robert Hanson is an UW-Madison-graduated virologist who had a position in the department of veterinary medicine. Initially he was interested in Newcastle Disease Virus (NDV),[59] but during the 1960s his interest was expanded into neurological disease in mink, due to the TME outbreak in the Wisconsin fur industry. With his doctoral student, Richard Marsh, he examined the host range, neuropathology, and physicochemical properties of this slow and unconventional presumed viral agent.[60] Hanson's colleagues in Wisconsin, Dieter Burger and G. R. Hartsough conducted aetiological studies on the outbreak of TME in 1963, and found that there were spongiform-like holes, similar to scrapie-infected sheep. In the conference held in Washington in 1964, they reported their findings, and suggested that it could be a scrapie-like disease.[61] At the same time, they heard the news from Gajdusek's laboratory in Washington that they had succeeded in transmitting kuru into chimpanzees.[62] They also attempted the same type of experiment to transmit TME into monkeys.[63]

From 1969, Marsh and Hanson undertook a comprehensive study aimed at identifying the physical and chemical properties of the TME agent. They found that TME was chemically indistinguishable from the scrapie agent.[64] During the early 1970s, Hanson and Marsh investigated various forms of TME neuropathogenesis,

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[58] **Rampton, S., J. Stauber** (1997) *op. cit.* note 27: 87

[59] Newcastle disease is a serious and commonly fatal disease of chickens caused by a paramyxovirus. Other avian species are also infected, but usually with less severe consequences. Man is also susceptible. In most developing countries Newcastle disease is the most important infectious disease affecting village chickens. Newcastle disease continues to pose a severe threat to the poultry industry in spite of the availability of several vaccines.

[60] **Yuill, t. M. and B. G. Easterday** (1996) 'Robert Paul Hanson', *Biographical Memoirs* **70**: 147

[61] **Burger, D. & Hartsough, G.R.** (1965) 'Transmissible Encephalopathy of Mink', D.C. Gajdusek, C.J. Gibbs Jr., & M. Alpers (eds) *Slow, latent, and temperate virus infections* (Washington: USDA): 197-305

[62] **Gajdusek, D.C., Gibbs, C.J., Alpers, M.** (1966) *op. cit.* note 35

[63] **Eckroade, R.J., Zu Rhein, G.M., Marsh, R.F., Hanson, R.P.** (1970) 'Transmissible mink encephalopathy: experimental transmission to the squirrel monkey', *Science* 169(950): 1088-90

[64] **Marsh, R.F. & R.P. Hanson** (1969) 'Physical and chemical properties of the transmissible mink encephalopathy agent', *Journal of Virology* 3: 176-180

attempted to characterize the agent, and made comparisons with the scrapie agent.[65] From those studies, they concluded that TME could be good animal model to investigate other similar human and animal diseases such as kuru, CJD, and scrapie.[66] At the same time, in collaboration with Edinburgh researcher Richard Kimberlin, Marsh discovered that hamsters were also susceptible to both TME and scrapie, and had a much shorter incubation time than mice, developing higher levels of infectivity (over 10,000 infectious units per gram of brain) than any other test animals.[67] By succeeding in infecting hamsters with TME and scrapie, they were able to establish a second animal model that would play an important role alongside the mouse scrapie model in subsequent research.

Although Richard Marsh focused on physicochemical features of TME and scrapie-related diseases, the UW-Madison team shared the view, articulated by Robert Hanson, that it is necessary to unite molecular and epidemiological concepts and techniques as a seamless continuum in the study of the host-virus-environment interaction. Acting on this principle, during the 1970s, Richard Marsh in particular led the TME research team in UW-Madison, and attempted to reveal the physicochemical nature of TME and scrapie. After constructing the hamster model as faster, more economical and biochemically friendly, Marsh collaborated with UC Riverside pathologist, Joseph Semancik, and launched a series of purification experiments in order to isolate the purified form of the scrapie agent.

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[65] **Marsh, R.F., Burger, D., Eckroade, R., Zu Rhein, G.M., Hanson, R.P.** (1969) 'A preliminary report on the experimental host range of the transmissible mink encephalopathy agent', *Journal of Infectious Diseases* 120(6): 713-9; **zu Rhein, G.M., Eckroade, R., Marsh, R.F.** (1971) 'Experimental transmissible mink encephalopathy (TME) in mink, monkey, and hamster. Electron microscopic studies', *Journal of Neuropathology & Experimental Neurology* 30(1): 124; **Hanson, R.P., Eckroade, R.J., Marsh, R.F., Zu Rhein, G.M., Kanitz, C.L., Gustafson, D.P.** (1971) 'Susceptibility of mink to sheep scrapie', *Science* 172(985): 859-61

[66] **Marsh, R.F.** (1972) 'Animal model of human disease: kuru, Creutzfeldt-Jakob disease (slow virus infections). Animal model: transmissible mink encephalopathy, scrapie-like disease of mink', *American Journal of Pathology* 69(1): 209-12

4. Research trends in the 1970s

As discussed above, there were four major research laboratories conducting scrapie-like disease research in the United States during the 1970s. Researchers of scrapie-like diseases began from different medical and veterinary interests and backgrounds. However, by the mid-1970s the different lines of American research that I have discussed had all converged under the umbrella of research into "unconventional slow viruses". Moreover, researchers shared similar aims even if the detailed contents of the experiments were various. They mainly focused on the isolation of the scrapie agent using a range of biochemical and biophysical methods.

It is interesting to note the role-played in this convergence by the adoption of the loosely defined term, "unconventional slow viruses". This loosely defined, fuzzy concept played an important heuristic role in the construction of new scientific knowledge. According to a medical historian, Ilana Lowy, such loosely defined imprecise terms may facilitate the constitution and the maintenance of heterogeneous interactions between distinct groups of scientists pursuing otherwise distinct research project and methodologies. Lowy suggests that such loose concepts may serve as "boundary concepts", a notion she develops from Susan Leigh Star's term, "boundary object". For Star, boundary objects are material objects that are conceptualised in ways "which are both plastic enough to adapt to local needs [...and] robust enough to maintain a common identity across sites". [68] This plasticity enables different groups of scientists to pursue quite disparate lines of research, and to conceptualise the object of that research in quite different ways, which nonetheless

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[67] **Kimberlin, R. H. & R. F. Marsh** (1975) 'Comparison of scrapie and transmissible mink encephalopathy in hamsters I: biochemical studies of brain during development of disease', *Journal of infectious disease* ***131***(2): 97-103

[68] **Star, Susan Leigh, James R. Griesemer** (1989 [1998]) 'Institutional ecology, "translations", and boundary objects: amateurs and professionals in Berkeley's Museum of Vertebrate Zoology, 1907-39', Biagioli, B. (ed) *The Science Studies Reader* (London: Routledge): 509. For details, see **Lowy, Ilana** (1992) 'The strength of loose concepts - boundary concepts, federative experimental strategies and disciplinary growth: the case of immunology', *History of Science 30*: 371-396. Lowy's argument tends to be read as implying that loose and imprecise concepts themselves served to determine map of scientific practice in general. However, such an idealistic reading is not intended here. As will be seen, with regard to the case of the unconventional slow virus, the imprecise concept was adopted by scientists because it served their own interests in collaboration and cooperation.

claiming to be working on the same thing. It may also permit communication and co-operation between these disparate groups in pursuit of common interests such as institutional solidarity or large-scale funding. Lowy extends this notion to include "boundary concepts" – purely conceptual constructs without immediate material referents, but which nonetheless make possible similar federative claims to be pursuing a common scientific interest.

The concept of "unconventional slow viruses" is a case in point. The vagueness of the term itself makes clear that this is indeed a loose concept, as too does the lack of specificity of the criteria for membership of this class of diseases. General family resemblance, in terms of aetiological and pathological characteristics, suffered for a disease to be included in this class. Thus at the height of this concept's currency during the 1960s and 1970s, it included a wide range of conditions - amyotrophic lateral sclerosis (ALS),[69] Aleutian disease of mink,[70] and multiple sclerosis, as well as scrapie, kuru and CJD – some of which would subsequently be confirmed as viral conditions while other would be recategorised as quite other forms of disease.[71] The

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[69] ALS is a progressive neurodegenerative disease that attacks nerve cells in the brain and the spinal cord. The progressive degeneration of the motor neurons in ALS eventually leads to their death. It is often referred to as "Lou Gehrig's disease".

[70] Aleutian disease (AD) was described in ranch-raised mink in 1956. The disease was so named because it was first found in mink with the Aleutian coat color gene. It has since been demonstrated that all color phases of mink are susceptible to the disease. Aleutian disease progresses slowly, taking up to one year before the mink manifests any symptoms. This has been shown to be caused by Aleutian Mink Disease Virus, or ADV, which is a parvovirus that infects mink, ferrets, raccoons, skunks, and possibly other Mustelidae.

[71] **Kurland, Leonard T.** (1965) 'Amyotrophic Lateral Sclerosis: a reappraisal', D.C. Gajdusek, C.J. Gibbs Jr., & M. Alpers (eds) *Slow, latent, and temperate virus infections* (Washington: USDA): 13-22; **Hirano, Asao** (1965) 'Pathology of Amyotrophic Lateral Sclerosis', D.C. Gajdusek, C.J. Gibbs Jr., & M. Alpers (eds) *Slow, latent, and temperate virus infections* (Washington: USDA): 23-38; **Gibbs, Jr., C.J. & Gajdusek, D.C.** (1965) 'Attempt to demonstrate a transmissible agent in kuru, amyotrophic lateral sclerosis, and other subacute and chronic progressive nervous system degenerations of man', D.C. Gajdusek, C.J. Gibbs Jr., & M. Alpers (eds) *Slow, latent, and temperate virus infections* (Washington: USDA): 39-48; **Field, E.J.** (1965) 'Some observations on the clinical immunology of multiple sclerosis', D.C. Gajdusek, C.J. Gibbs Jr., & M. Alpers (eds) *Slow, latent, and temperate virus infections* (Washington: USDA): 187-194; **Gorham, J.R., Leader, R.W. et al.** (1965) 'Some observations on the natural occurrence of Aleutian disease', D.C. Gajdusek, C.J. Gibbs Jr., & M. Alpers (eds) *Slow, latent, and temperate virus infections* (Washington: USDA): 279-286; **Leader, R.W., Gorham, J.R., Hanson, J.B., Burger, D.** (1965) 'Pathogenesis of Aleutian disease of mink', D.C. Gajdusek, C.J. Gibbs Jr., & M. Alpers (eds) *Slow, latent, and temperate virus infections* (Washington: USDA): 287-296; **Helmboldt, C.F., Kenyon, A.J., Dessel, B.H.** (1965)'The

concept of a family of unconventional slow viruses was thus not dictated by any unequivocal natural occurrences. Nor was the inclusion of a disease in that family even anything more than provisional and negotiable. Rather, acceptance of the concept, even as merely a working hypothesis, involved a leap of scientific faith – as is evident how Gajdusek's decision to pursue further virological research into kuru on the strength of Hadlow's observation, regarding it histological similarity to scrapie.[72] That so many scientists, working on such a wide range of diseases, were willing to take such a leap of faith must lead us to ask just what they saw as the advantages of such a move.

What were the advantages to be gained through developing the concept of unconventional slow viruses? A part of the answer may be that, in this context in the US, the various researchers all benefited from being part of a larger programme by pursuing this federative strategy. Rather than working in relative isolation on obscure diseases of Papuan New Guinea cannibalism (kuru) or the livestock of Wisconsin mink farmers (TME and AD) or sheep farmers in European countries (scrapie), they could now claim to be studying a family of diseases that embraces all these conditions. Indeed, the same family of diseases might also be extended to include other diseases of much greater human importance. The most ambitious claim to extend the concept to other diseases in order to gain advantages is found in Gajdusek's Nobel lecture in 1976, when he suggested that the concept of slow viruses might help to account for human chronic diseases from Parkinson's disease to Alzheimer's disease. He claimed that:

> The suspicion has been awakened that many other chronic diseases of man may be slow virus infections. Data have gradually accumulated both from the virus laboratory and from epidemiological studies, which suggest that multiple sclerosis and Parkinson's disease, desseminated lupus erythematosis and juvenile diabetes, polymyositis and some forms of chronic arthritis may be slow infections with a masked and possible defective virus as their causes. The study of kuru was carried on simultaneously with a parallel attack on multiple sclerosis, amyotrophic lateral sclerosis, and Parkinson's disease; in addition, other degenerative dementias such as

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comparative aspects of Aleutian mink disease (AD)', D.C. Gajdusek, C.J. Gibbs Jr., & M. Alpers (eds) *Slow, latent, and temperate virus infections* (Washington: USDA): 315-328

[72] **Rampton, S., J. Stauber** (1997) *op. cit.* note 27: 48

Alzheimer's disease, Pick's disease, Huntington's chorea and parkinsonism-dementia were also studied.[73]

The construction of the concept of unconventional slow viruses thus made it possible for scientists working on a variety of relatively obscure diseases of limited social and economic importance to claim that, potentially at least, their individual and collective efforts might hold the promise of significant improvements in human health and welfare. Such a claim brought immediate advantages to the researches, in terms of their own sense of the importance of their work, and their ability to sell that work to funding bodies. It did so, moreover, in ways that enabled the various researches to build on their previous scientific achievements, which also developing new lines of research that permitted greater cooperation and convergence.

One of the benefits of the "strength of weak concepts" is that they permit the continuance of distinct lines of research. The conceptual convergence around the loose concept of "unconventional slow viruses" permitted the continuance of methodological diversity in various research teams in the US. Under that concept, they were able to pursue often distinct lines of research, even perhaps based upon different disciplinary predispositions, including virological, pathological and genetic research. However, it is important that all these teams shared the assumption that what they were working on was some kind of virus. Virology, especially work on the physico-chemical constitution of viruses, was one of the most exciting and productive areas of development in American biomedical sciences at the time, including the polio triumph, and investment in the search for cancer viruses. It is notable, in this respect, that many of the slow virus researchers came from poliovirus research. For instance, Joseph Smadel sponsored Gajdusek's project, and Gajdusek himself trained under prominent poliovirus researchers like John Enders and Macfarlane Burnet. Moreover, Richard Carp of IBR and Carl Eklund of RML had previously conducted poliovirus research. The slow virus researchers tended to replicate the methods that had proved so fruitful in poliovirus and cancer virus research for their new project. This tendency can be found in the methods they used,

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[73] **Gajdusek, D.C.** (1977) 'Unconventional viruses and the origin and disappearance of kuru', *Science* 197 (4307): 948

e.g. Gajdusek's transmission experiments with primates, Carp's cell culture experiments, Eklund's bioassay methods of scrapie research, and so on. All of these were based on virological methods that had figured in poliovirus research in the 1950s.

Furthermore, by the mid-1970s, all the slow virus research teams were also beginning to shift a greater or lesser proportion of their research resources to look at the physico-chemical properties of the putative slow viruses using a variety of approaches including biochemistry. In particular, each group in the field launched their own project to isolate the infectious agent of scrapie. One clear example of this approach was Prusiner and Hadlow's team in the RML, who launched a series of purification experiments between 1974 and 1979. By using various methods of ultracentrifugation, his team gradually isolated small infectious particles from infected cells. Furthermore, other American teams adopted other established and novel techniques of virus research in their efforts to isolate the scrapie agent, including biochemical methods at Madison, electron microscopy at IBR, and radiobiology at NIH. Critically, the availability of increasingly standardised research tools in the form of mouse and hamster scrapie, facilitated a certain amount of collaborative exchange and movement between the various research groups involved. In other words, it helped to further consolidate and extend the federative strategy outlined above. Although the concept of the family of diseases was loosely defined, the methodologies that were used to investigate the nature of the putative agent became increasingly standardised.[74] The establishment of these standardised methodologies also provided a route by which others from outside the established slow virus networks. For instance, a Canadian scientist, Hyun J. Cho, who had used ultracentrifugation techniques to isolate the Aleutian Disease Virus in Mink, now launched a project to isolate scrapie agent. This brought him into contact with the Wisconsin group, who also had an interest in Aleutian Disease, and who sent him samples of scrapie-infected hamster tissues. Cho affirmed that he had succeeded in

[74] As Joan Fujimura points out in her work on the history of cancer research during the post-war era, standardised tools and methodologies played a key role in transforming biology into an experimental and analytic science. For more details, see **Fujimura, Joan H.** (1996) *Crafting*

isolating 14 nm virus-like particles from the scrapie-infected mouse brain.[75] At that time, many researchers were anxious to find infectious particles of scrapie agent. This was great news for researchers in this field, and the particles became known as "Cho particles". Subsequently, he went on to collaborate with the Compton researchers in the UK, though his findings were eventually invalidated by work at Compton, where researchers found the same particles in a normal brain.[76]

Another example of the standardised centrifuge experiment deserves mention. Around the same time, in Riverside, California, efforts to isolate the scrapie agent were made by Terry Malone, who was a PhD student of Joseph Semancik. The team collaborated with Richard Marsh and used complicated centrifugation methods and chemical treatments such as ammonium sulphate precipitation, enzymatic digestion, and gel electrophoresis.[77] As a result, they obtained two exciting experimental results Firstly, many scrapie experts believed that the scrapie agent was hard to separate from cell membrane fragments due to the stability of the intimate association of the agent with the membrane. However, Malone and her colleagues' work showed that prolonged centrifugation could produce membrane-free scrapie agent. In other words, such prolonged centrifugation can break the membrane structure, and smaller particles can be separated from the membrane. This was a very strong blow to the membrane theory. Secondly, this membrane-free agent was tested with enzymes such as D-Nase, which could break DNA structure and inactivate it, R-Nase for denaturing RNA, and Protease-K for digesting amino-acid chains. As a result of these enzymatic treatments, scrapie infectivity after exposure to D-nase was significantly decreased. However, R-Nase and Protease-K did not produce such a

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Science: a sociohistory of the quest for the genetics of cancer (Cambridge, MA: Harvard University Press)

[75] **Cho, H.J., A.S. Greig** (1975) 'Isolation of 14-nm virus-like particles from mouse brain infected with scrapie agent', *Nature 257*(5528): 685-686

[76] **Cho, H. J., A. S. Greig, et al.** (1977) 'Virus-like particles from both control and scrapie-affected mouse brain', *Nature* **267**(2 June, 1977): 459-460; Hunter remarks that "Cho had probably been somewhat unlucky in that some preparations from scrapie brain did seem to contain a lot more of the particles than did normal brain." (**Hunter, Gordon** (1992) *op. cit.* note 53: 28)

[77] **Malone, T. G., R. F. Marsh, et al.** (1978) 'Membrane-free scrapie activity', *Journal of Virology* **25**(3): 933-5; **Marsh, R. F., T. G. Malone, *et al.*** (1978) 'Evidence for an essential DNA component in the Scrapie agent', *Nature* 275 (5676): 146-7

significant decrease. This meant that there was a DNA component that could interact with D-Nase, and was vital for the agent to function. Thus, they concluded that the scrapie agent contains an essential DNA component.[78] This groundbreaking news also became controversial later.[79]

Finally, I would like to make one more point about how standard methodologies facilitate collaboration. It is notable that the collaborative networks of scrapie research also spanned the Atlantic. For example, there was collaboration on genetic and virological research between Kimberlin from Edinburgh and Marsh from Wisconsin in the mid 1970s, which would lead to the hamster model of scrapie and TME.[80] Interestingly, what is most striking is that collaboration and exchange of personnel also occurred between US groups and the Compton group in the UK. This contrasts with the British context, because relations between Edinburgh and Compton were very tense. As seen in the previous chapters, this was a result of fundamental disagreement over the nature of the agent and a competitive concern to formulate empirically and theoretically tight aetiological theories of scrapie, supported by divergent methodological approaches and institutional styles of practice. This effectively prevented collaboration between the British research teams. In contrast, while American researchers generally did not accept the controversial claims put forward by the Compton researchers regarding the non-involvement of nucleic acids in replication of the scrapie agent, they nonetheless had no difficulty in collaborating with the Compton team. This was because the American researchers were more interested than the Edinburgh researchers in the physico-chemical methods being pursued at Compton and in the kinds of data they produced; and because, unlike the Edinburgh team, they were able to dissociate those methods and

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[78] **Marsh, R. F., T. G. Malone, et al.** (1978) 'Evidence for an essential DNA component in the Scrapie agent', *Nature* 275 (5676): 147

[79] Later many researchers doubted her experimental result because nobody was able to repeat this work. At that time, she and her colleagues believed in the validity of her work. According to Hunter's recollection, it took a period of years before the claims were withdrawn. This is an interesting example for investigating why many scientists were enthusiastic about her work initially, but subsequently came to regard it as the premature conclusion of a junior worker. I will discuss this later.

[80] **Kimberlin, R. H. & R. F. Marsh** (1975) *op. cit.* note 67; **Marsh, R. F., R. H. Kimberlin** (1975) 'Comparison of scrapie and transmissible mink encephalopathy in hamsters II: clinical signs, pathology, and pathogenesis', *Journal of Infectious Diseases* ***131***(2): 104-110

data from the more controversial theoretical claims put forward by the Compton researchers.

5. Conclusion

As I have shown, there was a clear pattern of scrapie research in the US. Most researchers in America accepted a loosely defined concept of scrapie as an "unconventional slow virus", even though some researchers were doubtful of the concept. However, this imprecise concept could be adapted to refer to variety of local experiments, and facilitated cooperation between heterogeneous researchers. Consequently, various groups of scientists who were initially interested in different subjects gradually accepted the concept to describe their own work, chiefly because it enabled them to forge collegial links with other scientists and to make claims for the importance of their collective endeavour that went far beyond what they could claim individually.

This convergence around the concept of unconventional slow viruses was followed by a significant degree of methodological convergence. In general, scrapie tended to be adopted as the preferred laboratory model for research in this area. At the local level, they came increasingly to share standardised methods of purification and chemical treatment to isolate the putative agent of scrapie. Particularly the technique of ultracentrifugation was seen as a good indication of the convergent pattern of research in the US. In sharing such methods and research patterns, American researchers' work could overlap. For instance, Cho's group, Marsh-Semancik's group, and Prusiner's group appeared to have overlapping methods: centrifugation, sedimentation, gel electrophoresis, enzyme treatments, and so forth. By the late 1970s, some scientists such as Cho and Malone were claiming to have found the core particle of the agent, though such claims remained to be confirmed.

It is worth briefly contrasting the American situation with that in Britain. First, unlike in Britain, where research had focused on scrapie in its own right, in the US, scrapie was incorporated as a convenient laboratory model for research into a more general if rather vaguely defined family of diseases, the unconventional slow viruses.

Secondly, American research in this area was sustained, not because of the economic importance of any one disease in that family, as was the case with scrapie in Britain, but primarily because it built on the success of virology, and held out the possibility that that success may be extended to include other diseases. In other words, whereas scrapie research in Britain derived from agricultural demands and governmental responses, slow virus research in the US was initiated by the driving force of virological success.

The successful development of poliomyelitis vaccine in 1955 was widely regarded as a triumph of the virological approach in medical science. Huge amounts of money were invested and a large number of scientists involved. Consequently, the poliovirus research became a standard model for virology, and some scientists expected the success could be extended into other areas.[81] In this regard, it is notable that many researchers in the slow virus field worked or trained in the field of poliovirus research. It is not a coincidence that the most prominent poliovirus scientists, e.g. Enders, Smadel, Bernet, and Koprowski, were involved in the slow virus research directly and indirectly. Hilary Koprowski was also involved in setting up the scrapie advisory committee in Britain in 1958 and participated in the scrapie workshop at Washington in 1964.[82] Moreover, many researchers in this field came from the poliovirus research: as mentioned, Gajdusek was initially funded by the National Foundation for Infantile Paralysis shows the clear relationship between the two fields. He was trained by Enders, Smadel, and Bernet. Carp and Eklund also conducted poliovirus research before coming to the field of slow viruses.

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[81] There are many historical studies on poliovirus in America. **Gould, Tony** (1995) *A summer plague: polio and its survivors* (New Haven: Yale University Press); **Wilson, Daniel J.** (1998) 'A crippling fear: experiencing polio in the era of FDR', *Bulletin of the History of Medicine* 72 (3): 464-495; **Benison, Saul** (1976) 'Poliomyelitis and the Rockefeller Institute: social effects and institutional response', *Theory and practice in American medicine* (New York: Science History Publications): 85-103; **Blume, Stuart & Geesink, Ingrid** (2000)'A brief history of polio vaccines', *Science* 288 (5471):1593-1594; **Grimshaw, Margaret** (1995) 'Scientific specialization and the poliovirus controversy in the years before World War II', *Bulletin of the History of Medicine* 69 (1): 44-65; **Grimshaw, Margaret** (1996) *The poliovirus controversy in the years before World War II: shaping America's medical science approach to human disease* (PhD thesis: University California, Los Angeles). And also on Britain, **Hardy, Anne** (1997) 'Poliomyelitis and the neurologists: the view from England 1896-1966', *Bulletin of the History of Medicine* 71 (2): 249-272

The broadly virological consensus supported that feature of American scrapie research that contrasts most markedly with the British scene, namely the tendency for research to converge around a single set of concepts and methodologies. In Britain, as we have seen, relations between the two main groups of scrapie researchers quickly became strained and antagonistic. This was a consequence of a number of factors, including the very different disciplinary backgrounds from which the two groups came to scrapie research, and the different laboratory cultures they embodied. Also important, however, was the fact that scrapie was plainly a matter of considerable economic and social significance in Britain. Consequently, neither group needed to ally itself with others to assert the importance of its work. Rather, within a framework of unified research council administration with close links to central government and other policy bodies, there was a great deal at stake on maintaining the distinctiveness and ideally the dominance of one's own approach. As we have seen, this lay at the heart of the opposition between the Compton and Edinburgh groups over their divergent theoretical, methodological and cultural approaches to scrapie research. It is notable, however, that such factors did not hinder collaboration with American researchers. On the contrary, both British groups exchanged data, material and personnel quite freely with their American colleagues, just as the American centers exchanged such resources freely among themselves. In this broader international context, there was more to gain and less to lose by stressing convergence over divergence, and eclecticism over purity. This was certainly the case within the diversified setting of American researcher institutions, where a generalized commitment to virological methods was sufficient to motivate a remarkable convergence of different groups around the key topic of scrapie. But the same generalized interest in scrapie also made possible collaboration with British scientists, since it did not impinge on the particularly local interests that were responsible for the tensions and hostilities within the British system.

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[82] **Gajdusek, D.C.& Gibbs Jr., C.J., Alpers, M.** (1965) *Slow, latent and temperate virus infections* (Washington: USDA)

Chapter 7 – Formulating the prion hypothesis: Stanley Prusiner's work, 1972-1982

1. Introduction

In the early 1970s, a medical doctor from San Francisco, Stanley Prusiner, set up his own research laboratory to examine the chemical make-up of the scrapie agent. Although he was a relatively latecomer in the research field, he performed quite large-scale experimental work. Between 1974 and 1979, Prusiner conducted several experiments to purify the scrapie agent in collaboration with researchers in the Rocky Mountain Laboratory, Hamilton (RML). During this period, although he was not successful in isolating it in purified form, he did manage to obtain a partially purified form of the scrapie agent using centrifugation methods.

After completing the collaborative project with the RML researchers, he developed new methodologies for characterising the biochemical structure of the agent. In 1982, Prusiner published an article in *Science* magazine. The title was "Novel proteinaceous infectious particles cause scrapie" and here, for the first time, he called these particles "prions."[1] This eight-page long article caused an uproar in the scientific community. Many people read this paper as propounding a novel but heretical notion in the field of biological theory. For this reason, researchers and commentators furiously attacked this idea, believing it to violate the consensus that the only molecules capable of containing and replicating genetic information are nucleic acids. At the time, many people in the field interpreted Prusiner's article as arguing that transmissible disorders of the central nervous system, such as scrapie in sheep, Creutzfeldt-Jakob disease (CJD) and kuru in humans, could be caused by naked protein particles without nucleic acid. Stanley Prusiner, however, never acknowledged that this was what he had meant to convey. Notwithstanding this, some claimed that this idea could provide a significant clue to understanding one of

[1] **Prusiner, Stanley** (1982a) 'Novel proteinaceous infectious particles cause scrapie', *Science 216* (9 April 1982): 136-144

the most troublesome diseases in America, Alzheimer's. The resulting dispute between Prusiner and prion sceptics has continued for two decades.

In this chapter, I will describe how Prusiner first developed his basic experimental system for purifying scrapie agent with his collaborators at the RML. While many commentators consider the 1970s as a period of "false trail" or a "failure of purification", it was a significant time for Prusiner, who was able to generate systematic data from his large-scale physicochemical experiments. To conduct these systematic experiments he had to collaborate with other established groups of scientists. I will discuss how collaboration with scientists in the RML worked and to what extent the collaboration played a role in developing Prusiner's research career. His procedures for characterising the so-called "sedimentation profiles" of the scrapie agent will be elucidated and, from these profiles, how he came to speculate that the agent might be a hydrophobic protein.

In the later sections of this chapter, I will describe how Prusiner went on to elaborate his experimental system, in particular his methods of scrapie bioassay, in ways that greatly increased the efficiency of his experimental methods overall. Using these methods, Prusiner was able to produce yet more data on the biochemical characteristics of the scrapie agent, culminating in his high-profile publication in *Science* in 1982. I will conclude by discussing Prusiner's strategy of proposing the name "prion" in this paper, and by stressing in particular how he chose the name as a means of prioritising the importance of his own biochemical findings while carefully avoiding committing himself to any more general speculations about the biological nature of the agent.

2. Setting up a laboratory and collaboration with the RML

Between 1969 and 1972, Stanley Prusiner, who graduated from University of Pennsylvania, began his research career in San Francisco. He worked for the National Institutes of Health (NIH) as an intern on a Public Health Service (PHS) assignment instead of doing military service in the Vietnam War. He joined a laboratory of biochemistry where Earl Stadtman, a pioneer in the elucidation of the mechanism by

which enzymes are regulated, was a director. Stadtman became a mentor of Prusiner, and with him, Prusiner investigated glutaminases in *E. coli* in the lab. According to Prusiner's recollection, he learned an "immense amount about the research process; developing assays, purifying macromolecules, documenting a discovery by many approaches, and writing a clear manuscript describing what is known and what remains to be investigated."[2] During the 1970s, his work mainly focused on developing economical bioassay methods for enzymes, and how to purify the enzymes.[3] It seems that the skills he acquired in Earl Stadtman's lab played an important role in developing his research, as he acknowledges.[4] After completing his internship for the NIH, he began a residency in the University of California, San Francisco (UCSF) in the department of neurology. In this period, he encountered a female patient who was diagnosed as having Creutzfeldt-Jakob disease (CJD), which was known as a fatal neurological disorder in humans. According to his Nobel Lecture, this was the beginning of Prusiner's interest in this subject:

> In July 1972, I began a residency at the University of California San Francisco in the Department of Neurology. Two months later, I admitted a female patient who was exhibiting progressive loss of memory and difficulty performing some routine tasks. I was surprised to learn that she was dying of a "slow virus" infection called Creutzfeldt-Jakob disease (CJD) which evoked no response from the body's defenses. Next, I learned that scientists were unsure if a virus was really the cause of CJD since the causative infectious agent had some unusual properties. The amazing properties of the presumed causative "slow virus" captivated my imagination and I began to think that defining the molecular structure of this elusive agent might be a wonderful research project. The more that I read about CJD and the seemingly related diseases--kuru of the Fore people of New Guinea and scrapie of sheep--the more captivated I became.[5]

In 1974, Prusiner was offered an assistant professorship in the department of neurology, UCSF. He decided to set up a laboratory in order to examine the mysterious human disorder, CJD. However, he chose to work not on CJD itself, but

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[2] **Prusiner, Stanley B.** (1997) 'Autobiography', *Nobel e-Museum, The Official Web Site of The Nobel Foundation* (www.nobel.se/medicine/laureate/1997/prusiner-autobio.html): 2

[3] **Prusiner, S. B., Milner, L. S., Long, C. W., Myers, M. L.** (1971) 'Vacuum manifold for rapid assay of enzymes using radioactive tracers and ion exchange chromatography', *Review of Scientific Instruments 42* (4): 493-494

[4] **McManus, Rich** (1998) 'Nobelist Prusiner draws homecoming crowd', *NIH Record* (11 March, 1998: www.nih.gov/news/NIH-Record/11_03_98/story 02.htm): 1

[5] **Prusiner, Stanley B.** (1998) 'Prions', *PNAS 95*: 13363

on the supposedly similar disease of sheep, scrapie. He thought that this was "a wonderful problem for a chemist". In his interview with *Discovery* magazine in 1986, he claimed that "it had been attacked by pathologists, physicians, veterinarians. Those who tried to unravel the chemistry of the disease hadn't taken a very careful approach. I spent much of my time thinking about how I was going to do this problem. When I finished, I set up a lab here. I got some money from the neurology department, but not a lot."[6] There is an interesting anecdotal story related to his failure to secure an NIH grant. He recollects that the NIH said, "who the hell are you? You know something about enzyme chemistry, but you know nothing about virology, and nothing about scrapie, and you never trained with anybody."[7]

Prusiner was a latecomer to the field of scrapie research, and the small field was already occupied by many prominent researchers. For this reason, there was relatively small room to launch his project in the field. However, the territory of biochemical studies of scrapie was less developed as yet, because the area was known to be quite risky and not so productive at that time. For the past twelve years many researchers had tried and failed to achieve any clean data regarding its chemical structure. Thus, relatively small number of scientists was interested in this research area.

Prusiner had to overcome prejudice against a purely chemical approach, so he took a virology course in order to acquire virological knowledge of scrapie. More importantly, Prusiner realised that collaboration with current scrapie researchers was crucial to participate in the field. Consequently, he contacted researchers in the Rocky Mountain Laboratory (RML), William Hadlow and Carl Eklund. They were already well-established researchers in this field, and the RML was working on the laboratory-standard scrapie agents, obtained from Compton, England.[8] Furthermore,

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[6] **Taubes, Gary** (1986) 'The game of the name is fame. But is it science?', *Discovery* (December 1986): 31. This article was written for the purpose of criticising Prusiner's strategy of doing science in 1986, in the peak-time of the prion controversy. So it is not an impartial source. However, it contains a rare interview with Prusiner, so I used it primarily as a source of Prusiner's own quotes about his experimental work.

[7] *Ibid.*, 31.

[8] Since William Hadlow visited Compton laboratory in the early 1960s, they were able to maintain the scrapie agent, particularly as isolated by Chandler in 1961, in their laboratory in Hamilton, Montana. This agent was the main experimental material used by the majority of laboratories in the US during the 1970s.

the laboratory maintained a large animal stock for experimental purposes. For Prusiner, the RML was thus the ideal place to obtain the actual scrapie agent and conduct animal experiments. The RML researchers also had a great deal of experience and knowledge of scrapie, on which Prusiner was able to draw. According to him, Hadlow and Eklund taught him an immense amount about scrapie, and helped him initiate studies on the sedimentation behaviour of the scrapie agent.[9]

Collaboration can work well when both parties match their interests reciprocally. According to the analysis of a historian of science, Jane Maienschein, collaborations typically occur for one or more of three overlapping reasons: co-labouring, producing greater credibility, and creation of community.[10] The case of collaboration between Prusiner and the RML team can be seen as exemplifying this analysis. The collaboration began with Prusiner's contact with William Hadlow, and involved co-labouring between animal and biochemical work. The RML team also had some reasons to collaborate with Prusiner. Although Prusiner was a newcomer and had not much experience in dealing with scrapie, he was an expert in biochemistry and enzymology. From William Hadlow's point of view, the collaboration fulfilled the need for a biochemist for their new project. In the early 1970s, the RML launched a new project to isolate the agent. However, the RML team mainly consisted of veterinarians and virologists, so they needed a biochemist. According to Richard Race, who was a young researcher in the RML at that time and now retired, "basically Stan [Prusiner] did all of the physicochemical treatments. What we did here, he would come out, get the tissues, take them home [San Francisco], work them up and then send them back out, and then we would inoculate the mice to determine where the infectivity had gone".[11] The RML researchers dealt with mouse stocks and inoculation experiments, which were more or less related to conventional biological and virological work. On the other hand, Prusiner's lab was dealing with physico-chemical treatments: centrifugation, sedimentation, enzymatic treatments, and chemical treatments.

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[9] **Prusiner, S.B.** (1997) *op. cit.* note 2
[10] **Maienschein, Jane** (1993) 'Why Collaborate?', *Journal of History of Biology 26* (2): 167
[11] **Race, Richard** (2000) Interview with author (14 August 2000: Hamilton, Montana)

For Prusiner, there was another reason to collaborate with the RML. He was a relative beginner in the field and frustrated by not being able to raise research funds for his own project. He probably needed to gain credibility from this small but highly esoteric scientific community. As Maienschein suggests, collaborations among different individuals may produce greater credibility, because each brings to the project his or her own credentials and acceptability in a different research community.[12] Hadlow and his team in RML had already been established as one of the main scrapie research groups in the world, whereas Prusiner had only just set up his lab and failed to raise an NIH grant. As Prusiner stated, he collaborated with the RML team to "rebut the disapproval of my first NIH application on scrapie".[13] This is a clear example of gaining credibility by virtue of collaboration with another group.

3. Isolating the agent: sedimentation profile

Many writers only discuss the 1970s, during which period Prusiner was collaborating with the RML, as a period of trial and failure to isolate the scrapie agent. For instance, in his brief historical review, Gordon Hunter dubs this period "the period of false trails (1973-1981)".[14] Moreover, most historians focus on the post-prion era since 1982.[15] Prusiner's work at this time, meanwhile, is regarded as merely the preliminary stage to devising his famous "prion" theory. However, I do not think this does him justice. Actually, Prusiner's experimental work in this period played a crucial role in shaping his later ideas. His sedimentation profiles and physicochemical treatments led him to question the conventional suppositions about the presence of an informational molecule in the scrapie agent.

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[12] **Maienschein, Jane** (1993) *op. cit.* note 10: 167

[13] **Prusiner, Stanley B.** (1997) *op. cit.* note 2: 3

[14] **Hunter, Gordon** (1992) 'The searching for the scrapie agent: 1961-1981', Prusiner, S.B., J. Collinge et al. *Prion Diseases in Humans and Animals* (London: Ellis Horwood): 23-29

[15] Many writings on mad cow disease focus on the period after 1982, regarding this period as just a kind of pre-history of prion paradigm. Such claims can easily be found in several writings, see **Rhodes, R.** (1997) *Deadly Feast: Tracking the Secrets of a Terrifying New Plague.* (New York: Simon & Schuster); **Rampton, S., J. Stauber** (1997) *Mad Cow USA* (Common Courage Press); **Cooke, J.** (1998) ***Cannibals, Cows, and the CJD Catastrophe*** (London: Minerva); **Brouwer, Eve** (1998) 'Sheep to cows to man: a history of TSEs', Scott C. Ratzan (ed.) *The Cow Crisis: Health and the Public Good* (London: UCL Press): 26-34

As mentioned earlier, during the 1970s the main goal of American scrapie researchers came increasingly to be isolating the scrapie agent, though there were some huge obstacles, including long incubation period, difficulties of separating it from the cellular structure, and no visual evidence of the agent. From my survey, during the 1970s there were six major research groups doing scrapie work in North America: IBR in New York, RML in Montana, University of Wisconsin, Madison, Gajdusek's lab in NIH, Bethesda, Cho's group in Canada and Prusiner's lab in San Francisco. Five of these six groups launched similar projects for purifying the agent and examining its chemical structure.[16] Consequently, for Prusiner and his collaborators in Montana, purification of the scrapie agent was the right agenda with respect to the mainstream tendency in America. In this collaborative work, Prusiner showed an "almost monomaniacal zeal to isolate the scrapie agent".[17]

The process of purification was, and still is, one of the hardest tasks amongst scrapie researchers. The scrapie agent is obtained from infected brain tissues in which a wide variety of proteins, plus DNA and RNA are present. Since 1961, many attempts have been made to purify scrapie from cellular material on an assumption that the scrapie agent exists as a discrete particulate structure. However, as Richard Kimberlin, a scrapie expert in Edinburgh, remarked in 1976, these attempts had consistently failed, to the point where most workers in the field now believed that the original assumption may be wrong. This led researchers to suppose that it is usually very intimately bound up with membrane structure.[18] Indeed, some British scientists even hypothesised that it is an integral part of the membrane structure, and suggested the so-called "membrane theory". Consequently, the problem of isolating the agent increasingly came to be seen by researchers in the UK and US alike as one of purification of the agent from cell membrane fragments.

Prusiner's collaboration with the RML team marked a significant shift in his own way of working. Hitherto he had worked on developing quick and efficient methods

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[16] Only one of them, the Institute for Basic Research (IBR) in New York, was focusing on biological and pathogenic characteristics of scrapie at the time. However, even they had a small project to detect the scrapie agent by electro-microscope and chemical treatments. For more details, see the previous chapter on research into unconventional slow virus in the US.

[17] **Taubes, Gary** (1986) *op. cit.* note 6: 31

of bioassay for measuring enzyme activity. By contrast, the Prusiner-RML work involved a much slower form of bioassay (i.e. titration of the agent in mice) that took a year to conduct. This represented a significant investment of time and effort in what might prove an unsuccessful attempt to purify the agent, and is an indication of Prusiner's commitment to the scrapie work. During his collaboration with the RML team, Prusiner used as many as 250,000 laboratory mice.[19]

The basic procedure of purification is as follows; Prusiner worked with homogenized samples of spleen and brain from scrapie-infected mice. This homogenate consisted of a wide range of cell components of different sizes and chemical constitution, including, presumably, the scrapie agent. Prusiner and his colleagues' basic method was to separate this mixture into different fractions using the established method of differential centrifugation. (See Figure 1)

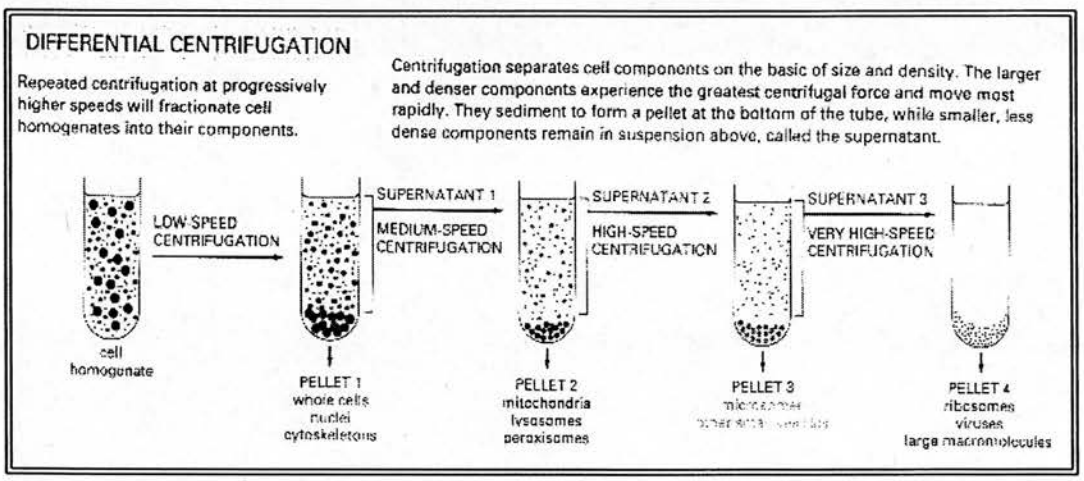

Figure 1: Differential centrifugation[20]

This centrifugation and sedimentation process was well established as a standard process for separating different sub-cellular components from homogenised cells. The homogenate, which contains all kinds of cell fractions, is placed in test tubes and rotated at different speeds and for different durations in a centrifuge. Once the samples have been centrifuged, the cellular homogenate is divided into two parts;

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[18] **Kimberlin, Richard** (1976) 'Experimental scrapie in the mouse: a review of an important model disease', *Science Progress 63*: 466

[19] **Taubes, Gary** (1986) *op. cit. note* 6: 31

[20] *Ibid.*,161

the larger and denser components are sedimented to form a pellet (P) at the bottom of the test tubes, while the smaller and lighter components remain in suspension in the supernatant.[21]

The different fractions of scrapie-infected brain and spleen were then tested for the presence of the scrapie agent using the standard method of titration of infectivity in mice, as discussed in earlier chapters. The resulting picture of the variation of infectivity across the different sedimentation fractions was called the sedimentation profile. By identifying those fractions in which scrapie infectivity was concentrated, and by then subjecting those fractions to further fractionation and again testing for infectivity, Prusiner hoped ultimately to produce what would effectively be a pure preparation of the scrapie agent.

This was essentially a very hit-and-miss procedure, involving trial-and-error to discover what speeds and durations of centrifugation were most effective in sedimenting out different components of the homogenate, and it involved a huge amount of tedious and repetitive work. In the end, however, after five years of work and the sacrifice of 250,000 mice, Prusiner and his collaborators were able to identify a particular fragment of the homogenate – called P5, the pellet produced by the fifth sequential centrifugation of a sample of homogenate – that contained 50-80% of the infectious activity of the original material.

The production of this homogenate fraction P5 marked an important stage in the development of Prusiner's research. Prusiner did not suppose that P5 consisted of pure scrapie agent, but he regarded it as a partial purification that went significantly beyond anything that had been achieved previously. A wide variety of cellular components were removed by the sequential centrifugation, and P5 consisted of particles smaller than mitochondria and larger than soluble proteins – including, Prusiner supposed, the scrapie agent.[22] Importantly, P5 was devoid of cellular membrane fragments, showing for the first time that the scrapie agent could be obtained in a form that was not bound up with cellular membranes.

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[21] **Albert, Bruce, Dennis Bray et al.** (1998) *Essential Cell biology* (London: Garland Publishing): 161

[22] **Prusiner, S. B., W. J. Hadlow, et al.** (1978) 'Partial purification and evidence for multiple molecular forms of the scrapie agent', *Biochemistry* **17**(23): 4993-9

One of the implications of Prusiner's claim to have produced membrane-free scrapie agent was that the membrane hypothesis could no longer be sustained. As shown in chapter 4, researchers at Compton, England, had hypothesised that replication of the agent might depend on its close association with intact and functional plasma membrane. This idea was suggested by two prominent biochemists at Compton, Gordon Hunter and Richard Gibbons in 1967.[23] Around the same time, David Haig and Tikvah Alper supported this hypothesis by showing their experimental results of the irradiation of the scrapie agent.[24] Prusiner's demonstration of infectivity in membrane-free preparations of the agent was at odds with this hypothesis. Moreover, his claim to have produced such a membrane-free preparation was reinforced by additional experimental work. Some of his samples of mouse scrapie homogenate were subjected to treatment with ultrasound and 0.5% DOC (sodium deoxycholate) before centrifugation. The former has been used for breaking cellular membranes with high frequency sound,[25] and the latter was known as a detergent disrupting cellular membranes.[26] This treatment, Prusiner argued, ensured that no functionally intact plasma membrane was present in these samples. If the membrane hypothesis was true, the sedimentation profile of these samples – i.e. the pattern of infectivity in the various sedimentation fractions – should have differed markedly from that in non-treated homogenate. However, Prusiner showed that treatment with ultrasound and DOC made little difference to the sedimentation profile. The work of Prusiner and his collaborators showed that infectivity, in other words, was independent of the presence of intact plasma membranes. As a result of their experiments, the membrane hypothesis was shown to be inadequate to explain the complicated mechanism of the disease.

Perhaps more importantly for Prusiner, the production of fraction P5 now provided him with a preparation of the scrapie agent on which he could perform

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[23] **Gibbons, R. A. and G. D. Hunter** (1967) 'Nature of scrapie agent', *Nature* **215** (2 Sept. 1967): 1041-1043

[24] **Alper, T., W.A. Cramp, et al.** (1967) 'Does the agent of scrapie replicate without nucleic acid?', *Nature* **214** (20 May, 1967): 764-766

[25] **Albert, Bruce, Dennis Bray et al.** (1998) *op. cit.* note 20: 160

[26] **Prusiner, S. B., W. J. Hadlow, et al.** (1977) 'Sedimentation properties of the scrapie agent', *PNAS* **74** (10): 4659

further biochemical research in the absence of any protective or otherwise confusing influence arising from its intimate association with the plasma membrane.

4. The hydrophobic character of the scrapie agent

Having obtained this partially purified form of the scrapie agent, Prusiner launched experiments to examine its physicochemical make-up. One of the most unusual properties of the scrapie agent is its remarkable heat stability. Several investigators had attempted to inactivate the infectivity of the agent by heating, but these attempts had shown that the agent is completely stable at temperatures as high as 80 degrees.[27] Prusiner repeated this heating experiment with his partially purified samples. The results were striking. For one thing, he confirmed that the agent is remarkably heat resistant. Moreover, when the agent was heated, the size of the agent as measured using sucrose gradient centrifugation appeared to increase.

Prusiner proposed two interpretations of these phenomena. One possible explanation for the heat resistance is that the scrapie agent is similar to a parvovirus, which is known to be more stable than most other biological molecular structures to heat. In fact relatively few biological particles are stable in the situation of heating, and most conventional viruses are destroyed. Parvoviruses, which are small single-stranded DNA viruses, are the most heat-resistant. Similarity to a parvovirus would also explain other properties of scrapie agent such as its resistance to nuclease digestion if, like parvoviruses, it consists of single-stranded DNA protected by a protein and/or lipid coat.[28] But importantly, similarity to a parvovirus would not explain the apparent increase in molecular weight on heating.

Consequently, Prusiner proposed a more novel explanation, based on wider speculations about the biochemical character of the scrapie agent. He started from what was generally known about the strong tendency for the agent to associate itself

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[27] **Gordon, W. S.** (1957) 'The opening discussion to Palmer's paper', *The Veterinary Record* **69** (7, Dec. 1957): 1324-1327; **Millson, G. C., G. D. Hunter, et al.** (1976) 'The physico-chemical nature of the scrapie agent', R. H. Kimberlin (ed.) *Slow Virus Diseases of Animals and Man* (Oxford: North-Holland Publishing Co.): 243-266

[28] **Prusiner, S. B., W. J. Hadlow, et al.** (1978) 'Sedimentation characteristics of the scrapie agent from murine spleen and brain', *Biochemistry* **17** (23): 4992

with cell membranes. Cell membranes consist of a phospholipid bilayer, with a hydrophobic (water-hating) middle layer and hydrophilic (water-loving) outer layer. In an aqueous environment, the hydrophobic lipid chains of phospholipid molecules tend to be forced together, while the hydrophilic phosphate components tend to face outwards, where they can form hydrogen bonds with water. This produces a particular three-dimensional structure, called a phospholipid bilayer, which is the basic structure of cellular membranes.

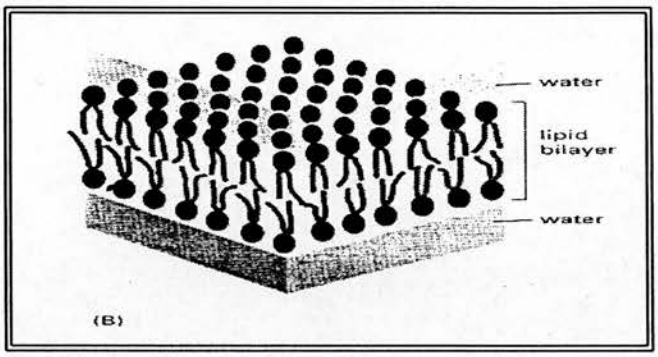

Figure 2: Schematic drawing of a phospholipid bilayer in water; the water-hating tails avoid the water and water-loving components face the water.[29]

Prusiner suggested that the strong association of scrapie agent with such membranes might be explained if it had a hydrophobic surface, such that it would tend to avoid water by inserting itself into the hydrophobic mid-layer of the membrane. The same hydrophobic property could also be invoked to explain the increase in size of membrane-free infectious particles on heating. In an aqueous environment, hydrophobic particles will tend to aggregate together. Indeed, Linus Pauling, who won the Nobel Prize for his protein work, had shown that these sorts of hydrophobic interactions increase on heating.[30] Consequently, Prusiner speculated that the increase in size of particles of scrapie agent on heating could be due to their increasing aggregation as a result of hydrophobic interactions. Indeed, he went on to propose that the agent itself might be a hydrophobic protein.

Prusiner also pointed out that a number of the other peculiar properties of the scrapie agent might be explained if it turned out to be a hydrophobic protein:

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[29] *Ibid.*, 351

[30] **Pauling, Linus** (1960) *The Nature of the Chemical Bond* (Ithaca: Cornell University Press)

> first, the unusual stability of the agent to heating is consistent with such a view since hydrophobic interactions are stabilised at high temperature. Second, the association of the scrapie agent with membrane fraction is understandable since hydrophobic proteins can readily insert themselves into membranes. Third, not unlike experiences with the scrapie agent, many hydrophobic proteins have been found to be exceedingly difficult to purify with retention of activity. Fourth, the scrapie agent like many lipoproteins appears to exhibit minimal antigenicity in contrast to apolipoproteins, which are often good antigens. Fifth, the apparent discrepancy in the size of the agent as determined by ultrafilteration and by ionising radiation might be due to the ability of the agent to undergo aggregation and dissociation as a consequence of its hydrophobic surface.[31]

In other words, this hypothesis seems to answer many mysterious problems of the scrapie agent: heat stability; strong membrane association; difficulty of purification; absence of antigenic reaction; difficulty in determining the size of the agent.

Prusiner's idea that the scrapie agent might be a hydrophobic protein was highly speculative, being based, not on any direct observational data, but rather on the various peculiar properties of the agent that such a hypothesis would help to explain. It was also distinctly at odds with prevailing views about the biology of infectious agents in general, which are generally assumed to include some kind of nucleic acid genome. Consequently, Prusiner's arguments found little support from other researchers at that time. Although he later remarked, "I had anticipated that the purified scrapie agent would turn out to be a small virus, and was puzzled when the data kept telling me that our preparations contained protein but not nucleic acid",[32] at the time, his experimental data were insufficient to support any strong claim that there was only protein in the agent. The same data could have been interpreted differently by other people who had different views. Other researchers continued to suppose that the agent was most probably some kind of single-stranded virus. For instance, Laura Manuelidis, one of the leading CJD experts at the Yale medical school, still believes that the agent has quite similar properties to such viruses.[33] Furthermore, some researchers such as Gordon Hunter and Richard Kimberlin

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[31] **Prusiner, S. B., W. J. Hadlow, et al.** (1978) *op. cit.* note 22: 4998

[32] **Prusiner, S.B.** (1997) *op. cit.* note 2

[33] **Manuelidis, L.** (1996) 'In the community of dinosaurs: the viral view', L. Court and B. Dodet (eds) *Transmissible Subacute Spongiform Encephalopathies: Prion Diseases* (Paris: Elsevier): 375-390

thought that the hypothetical hydrophobicity of the agent was not a primary issue compared to phenomena such as strain variation which implied the presence of nucleic acid in the agent. Both Kimberlin and Hunter pointed out that this phenomenon of increasing size with heating might indicate the existence of glycoprotein as a component of the agent.[34] Nonetheless, as we shall see, Prusiner was evidently strongly attracted by the subject of the hypothesis of hydrophobic protein, and would devote an increasingly large proportion of his time and other resources to pursuing it.

5. End of the RML collaboration and Prusiner's methodological innovation

The first phase of Prusiner's work on scrapie came to an end when the NIH decided to close down the collaborative research with the RML. This was partly because the collaborative research consumed so much of the Institute's resources, and partly because the NIH had decided to reorientate research at the RML. Prusiner remarked that "we rapidly went through our ten thousand mice and even if we were handed money on a silver platter, we couldn't go on like that." According to Richard Race, the closing down of the project was due to a new orientation of research in the RML. Though the quotation is slightly long, it gives a good explanation of why the project was closed down in 1979:

> It broke down for political reasons in the late 1970s. There was kind of a change in the hierarchy at NIAID [the National Institute of Allergy and Infectious Diseases, which is a governing institute of the Rocky Mountain Laboratory]. We had a new scientific director, and they did not believe that the level of collaboration was mutual enough to warrant us using our facility to do all of the animal work. So they basically said we don't want to be doing Dr. Prusiner's animal work. Unless this was more of collaboration on a scientific level, we don't think that we should be involved to the extent that we are. So that kind of shut that part down...[It was] because they wanted the facility; the facility is limited, so if other people needed it who were here, they wanted it for the people that were here, not for people that were around the world. Today there are dozens of people who would love to collaborate with us just because we have the expertise to do the animal work. But we have enough in house people

[34] **Hunter, G. D., R. H. Kimberlin, et al.** (1973) 'Viral and non-viral properties of the scrapie agent', *Annals of Clinical Research* 5 (5): 262-7

working directly on the problem that are NIAID people that want to use the facility, so that is the way that it is done. [35]

About this time, Prusiner also had other troubles to contend with. His post in the Howard Hughes Medical Institute (HHMI) of UCSF was not renewed. However, fortunately, Prusiner recollects, "the tenure decision was reversed and I was able to continue my work. Although my work was never supported by HHMI again, I was extremely fortunate to receive much larger funding from the R. J. Reynolds Company through a program administered by Fred Saitz and Maclyn McCarthy, and shortly thereafter from the Sherman Fairchild Foundation under the direction of Walter Burke. While the vast majority of my funding always came from the NIH, these private sources were crucial in providing funds for the infrastructure which was the thousands of mice and hamsters that were mandatory."[36] In 1978, when the NIH decided to close the scrapie project down in the RML, Prusiner and his collaborators thought they should publish their provisional data. The volume was published in 1979.

With the ending of the RML work, Prusiner was effectively deprived of facilities for conducting bioassays of the various scrapie materials that he had been isolating and subjecting to other kinds of physico-chemical treatment. However, his new funds from R. J. Reynolds Company and the Sherman Fairchild Foundation now enabled him to plan new facilities at UCSF. Since he was starting from scratch in planning these facilities, he was also aware that the bioassay method employed at RML – i.e. titrating the infectivity of scrapie material in mice – was both slow and uneconomical in the sense that it required huge numbers of mice. In the late 1970s, however, Prusiner was able to devise new bioassay methods that improved enormously on the earlier method both in terms of speed and economy.

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[35] **Race, Richard** (2000) *op. cit.* note 11

[36] **Prusiner, S.B.** (1997) *op. cit.* note 2: 3. This is the very interesting story of how he raised funds from the big tobacco company, R. J. Reynolds, and from the Sherman Fairchild Foundation, which was founded by a big airline company, AMR. Every year the foundations provide huge amounts of money for medical research. Although the process of getting funds is an interesting story for social scientists, it is hard to obtain information about private funds. Thus, I merely mention the fact that he got funding from those leading private companies during the 1970s.

In 1975, Richard Kimberlin and Richard Marsh in the veterinary school of University of Wisconsin, Madison, collaborated to transmit scrapie and Transmissible Mink Encephalopathy (TME), another scrapie-like disease of minks, into Syrian hamsters.[37] From this experiment, Kimberlin and Marsh had noticed that the incubation period was much shorter than in mice.[38] In an article in 1977, Kimberlin suggested that hamster-adapted scrapie could be an alternative model for research. He argued in the article:

> We suggest that this scrapie model may be of general use in checking the validity of key findings from studies of mouse scrapie. We also suggest that 'Chandler' scrapie in hamsters offers some unique advantages to scrapie research, studies alone or in addition to some of the models of mouse scrapie...two particular advantages of this hamster scrapie model are the high infectivity titres in brain in the clinical stage of the disease, and the very short incubation period after intracerebral infection.[39]

Prusiner was evidently impressed by the possible short incubation period of scrapie in hamsters. While he was in contact with Richard Marsh around 1978 and 1979, Prusiner conducted his own investigations, which showed that the incubation period was only 60 days on average in hamsters, whereas the average incubation period of mouse scrapie was around 150 days.[40]

Prusiner's interest in hamster scrapie related to his research priorities. For scientists who took a more widely biological view of scrapie, including an interest in the processes of pathogenesis, hamster scrapie was an interesting novelty, but did not herald a particularly significant new line of research. Rather, for such workers, there was more to be gained by continuing to work with mice. Mouse scrapie was already characterised in considerable detail, including how it varied in different

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[37] **Kimberlin, R. H., R. F. Marsh** (1975) 'Comparison of scrapie and transmissible mink encephalopathy in hamsters I: biochemical studies of brain during development of disease', *Journal of infectious disease* ***131***(2): 97-103

[38] **Marsh, R. F., R. H. Kimberlin** (1975) 'Comparison of scrapie and transmissible mink encephalopathy in hamsters II: clinical signs, pathology, and pathogenesis', *Journal of Infectious Diseases* ***131***(2): 104-110

[39] **Kimberlin, R. H., C. A. Walker** (1977) 'Characteristics of a short incubation model of scrapie in the golden hamster', *Journal of General Virology* ***34***: 302

[40] **Prusiner, S. B., S. P. Cochran, et al.** (1981) 'Determination of scrapie agent titer from incubation period measurements in hamsters', S. Wayne, J., M. N. Hart, J. Stein-Streilein, W. R. Duncan and R. E. Billingham (eds) *Symposium on Hamster Immune Responsiveness and Experimental Models of Infectious and Oncologic Diseases*, (New York: Plenum Press): 385-399

strains of mice and using different strains of the scrapie agent. Consequently, it was seen to offer more scope for studying the biological processes of disease transmission and progression. In the case of hamster scrapie, on the other hand, only one strain of scrapie had been isolated, and little had been done to characterise the processes of pathogenesis.[41] Thus, the scope for further research was limited with this animal model.

By contrast, Prusiner was not interested in the biology or pathology of the disease, but only in the biochemistry of the agent at the time. Consequently, he was inclined to regard the host, be it mouse or hamster, as little more than a laboratory medium in which to conduct his bioassays of the agent. From this perspective, the fact that the hamsters delivered results more quickly than mice was a good enough reason to develop this method. A researcher in the RML, Suzette Priola, explains the differences between the two models: "we have a strain of hamster scrapie that goes very quickly. This is one advantage. It just takes 90 days to do an experiment. As opposed to the shortest natural model, experimental mouse model, which is 150 days. So, the advantage is usually time. In terms of doing pathogenesis or looking at where it is in the animal, mice are usually used more, because you can use more of them."[42] Undoubtedly, there is a huge advantage in using the hamster model for bioassay purposes: much shorter incubation period than mouse scrapie.

Moreover, the decision to use hamsters also enabled Prusiner to adopt another methodological innovation. It was his new method of titrating infectivity. Since Richard Chandler transmitted the agent into mice in 1961,[43] the titration of infectivity in mice had employed the so-called "end-point method". This method involves making a sequence of dilutions of the scrapie material, inoculating them into mice, and observing at what dilution 50% of the mice become infected. From this, it is possible to estimate the concentration of infectious particles in the original sample. Figure 3 shows the process of titrating infectivity by this method.

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[41] **Kimberlin, R. H., C. A. Walker** (1978) 'Evidence that the transmission of one source of scrapie agent to hamsters involves separation of agent strains from a mixture', *Journal of General Virology* **39**: 487-496

[42] **Priola, Suzette** (2000) Interview with author (RML, Hamilton, MT: 11 August 2000)

[43] **Chandler, R. L.** (1961) 'Encephalopathy in mice produced by inoculation with scrapie brain material', *The Lancet* **1**: 1378-1379

This method has advantages and disadvantages. Although it takes a long time, it was thought to produce an accurate indication of how much infectious substance is in the sample. This has been widely accepted as the standard bioassay method, not just for scrapie but also for viruses. On the other hand, this method is both wasteful and slow: wasteful, because several dilutions of each sample of scrapie material have to be tested in batches of mice, and slow, because the incubation time of the disease increases as the concentration of infectious material decreases. The end-point titration works with low concentrations, i.e. low enough to infect only 50% of the mice into which they are inoculated, at which point incubation can take as long as a year. Prusiner became aware of these disadvantages of the old method when he conducted his collaborative project with the RML researchers. He claimed that "although end-point titration in mice was an improvement over work in sheep and goats, this method of measuring the scrapie agent was still slower and more cumbersome than the methods used by Pasteur in his studies of viruses almost a century earlier."[44]

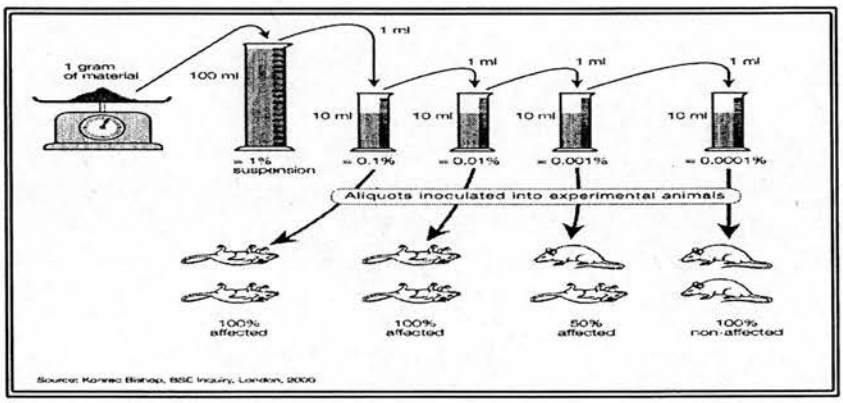

Figure 3: Titration - A known mass of material is homogenised in a saline solution to produce a 1 % suspension. After mixing, an aliquot is removed and diluted tenfold, to produce a 0.1% solution. This procedure is repeated until the required dilution is reached. Aliquots of the required dilutions are then injected into experimental animals. The dilution (titre) which produces 50 % affected animals is the ID_{50} dilution, referred to as 1 unit of infectivity. This can also be expressed in terms of the equivalent weight of the starting material. [45]

In 1978, Prusiner and his colleagues developed an alternative to the end-point titration. As early as 1963, Gordon Hunter observed an inverse relationship between

[44] **Prusiner, Stanley** (1984) 'Prions', *Scientific American 251* (October 1984): 50
[45] **BSE Inquiry** (2001) *The BSE Inquiry: Report Vol. 2* (London: The BSE Inquiry): *19*

concentration and incubation time, and suggested that this might provide an alternative method of measuring concentration.[46] If a standardised graph of the relationship between concentration and incubation time could be drawn, then it would be possible to calculate the concentration of infectious agent in any scrapie sample by simply measuring the incubation time. This would have the advantage that mice would only need to be inoculated with a single undiluted sample of scrapie material, so it would be far less wasteful of mice. Moreover, if that sample contained a relatively high concentration of scrapie agent, the time taken to deliver a result would be much shorter than at the low concentrations needed to conduct an end-point titration. However, Hunter and his colleagues were unsure about the accuracy of this method.[47] Soon after the trial in Compton, further tests in Edinburgh confirmed that it was inaccurate.[48]

Learning of this work in the course of this research into hamster scrapie, Prusiner investigated whether the incubation period might provide a better means of estimating the concentration of infectious material in hamsters than in mice. He confirmed that as in mice it is possible to correlate concentration with incubation period. With higher doses of the agent shorter incubation periods were observed. This inverse proportional (linear) relation could be systematically specified, such that the titre of a sample could be calculated from the incubation time of that sample (see Figure 4). He showed that, with relatively high concentrations of scrapie agent, that concentration could be measured in as little as 60 days and using only four hamsters.[49] Results could be achieved very rapidly with this method, and the number of laboratory animals used could be readily reduced. Previously, researchers would have to observe 60 laboratory mice for at least a year to determine the concentration

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[46] **Hunter, G. D., G.C. Millson, et al.** (1963) 'Observations on the comparative infectivity of cellular factions derived from homogenates of mouse-scrapie brain', *Research in Veterinary Science* **4**: 543-549

[47] *Ibid.*, 548

[48] **Dickinson, A. G., V. M. Meikle, et al.** (1968) 'Identification of a gene which controls the incubation period of some strains of scrapie agent in mice', *Journal of Comparative Pathology* **78**(3): 293-299; **Dickinson, A. G. and V. M. E. Meikle** (1969) 'Genetical control of the concentration of ME7 scrapie agent in the brain of mice', *Journal of the Comparative Pathology* **79**: 15-22

[49] **Prusiner, S. B., S. P. Cochran, et al.** (1982) 'Measurement of the scrapie agent using an incubation time interval assay', *Annals of Neurology* **11**(4): 353-8

with the end-point titration. However, using Prusiner's methods, they could assay a sample with just four animals in 60 days.

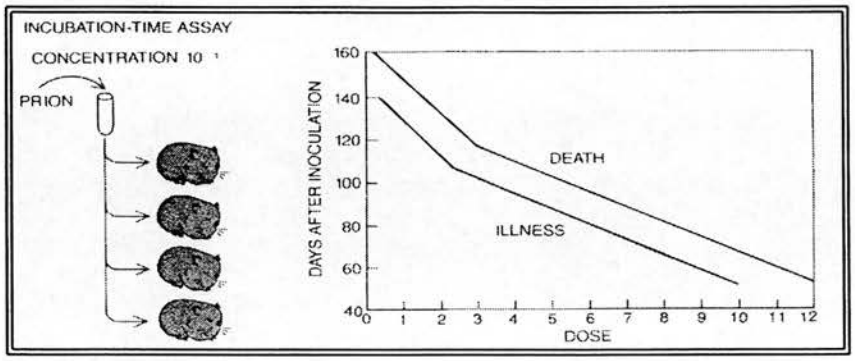

Figure 4. Incubation time titration[50]

However, others objected that this method included many potential sources of error. As soon as Prusiner gave publicity to the effectiveness of incubation time titration, researchers in the Institute of Basic Research (IBR), New York, scrutinised its validity, and showed error might occur unless other variables were controlled by means of end-point titration.[51] The director of the microbiology department in IBR, Richard Carp, urged that incubation time titration is efficient but it is not always accurate. He continues, "the fact that sometimes the treatment of the material that goes in it at a -1 or –2 dilution, can affect the relationship between incubation period and end-point titration...if you modify that treatment with a different detergent or a different solvent, or something that is different, then I think that you can upset that relationship between incubation period and titre and get a false reading on the total titre."[52] This problem of inaccuracy being caused by uncontrolled variables seems to be widely accepted. Even Richard Race in RML, a former Prusiner collaborator during the 1970s, pointed out that where a linear curve between dose and incubation time obtained, then the method would be fine. But if a non-linear curve was established, it would not be possible to interpret what is going on.[53] From these arguments, it can be summarised that Prusiner's novel method may be effective with

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[50] *Ibid.*, 53

[51] **Somerville, R. A., R. I. Carp** (1983) 'Altered scrapie infectivity estimates by titration and incubation period in the presence of detergents', *Journal of General Virology* **64**: 2045-2050

[52] **Carp, Richard** (2000) Interview with author (IBR, New York: 27 July, 2000)

[53] **Race, Richard** (2000) *op. cit.* note 11

respect to saving time and money, but that caution needs to be exercised when judging the accuracy of the results. However, Byron Caughey, who is a biochemist in RML, argues that the method is acceptable where fairly rough-and–ready estimates of infectivity performed under standardised conditions will suffice:

> It all depends on the kind of information that we need. If we need a quantitative assessment, a quantitative comparison of the amount of infectivity there, we prefer the endpoint dilution assay, though it is much more expensive and time consuming. The incubation time assay can be helpful and useful under certain circumstances, where you have a very well established standard curve between the actual endpoint dilution titre and the incubation period. But any time you are crossing species barriers or permuting the agents or manipulating it so that you create a different set of conditions or you are working in a different species, or anything like that where the standard curve may not work anymore; or you simply manipulated your samples in certain ways, biochemically, so that you don't know if the standard curve applies any more, you have to go back to the endpoint dilution assay. So, as often as possible, when it is really critical to get a quantitative comparison of titres, for whatever purpose, we prefer to use the endpoint dilution.[54]

Nonetheless, Prusiner judged incubation time titration to be quite adequate for his own needs, and adopted it as his standard method of scrapie bioassay. This methodological innovation proved to be a key factor in Prusiner's ability to make an impact on research into the biochemical nature of the scrapie agent. Between 1978 and 1982, he and his team were able to perform large numbers of experiments, generating a large body of data that would eventually enable them to make novel claims about the nature of the agent. At the interview with Gary Taubes in 1986, Prusiner claimed that over the next two or three years, "we did more experiments on the biochemistry of scrapie than everyone else in the history of scrapie combined."[55]

6. Biochemical investigations

Meanwhile, Prusiner was exploring other ways of moving forwards from the only partially successful attempts to isolate the scrapie agent that he had pursued at RML. After termination of the collaborative project, he set out alone to work on his own project. He met Richard Marsh in Wisconsin, and he went to Gajdusek, who won the

[54] **Caughey, Byron** (2000) Interview with author (RML, Hamilton, MT: 11 August 2000)

Nobel Prize with kuru research in 1976. According to Prusiner's colleague, Stephen DeArmond, "he did everything possible to learn how to approach the problem."[56] During the late 1970s, he attempted to extend his network and knowledge enthusiastically. Particularly, in 1978 and 1980, he "pilgrimaged to the Eastern Highlands [of Papua New Guinea] to add kuru to his quiver"[57]. On this trip, he worked up clinical studies on fifteen kuru patients with Gajdusek and Mike Alpers.

Above all, however, Prusiner was intrigued by the suggestions he had already made as a result of the RML work, that the scrapie agent is primarily or even exclusively proteinaceous in character. In 1979, he began to pursue a variety of biochemical experiments to throw further light on the involvement of proteins and of nucleic acids in the infectious activity of the scrapie agent. He considered the method of preparing a partially purified preparation of scrapie agent that he had developed with the RML researchers to be good enough to provide material for such experiments, and his aim now shifted to characterising this partially purified agent biochemically.

Around 1979, Prusiner set about testing the effects of a wide range of biochemical reagents on the scrapie agent, and specifically observing how various reagents affected the infectivity of the agent. Thanks to his new technique of hamster incubation time bioassay, Prusiner was able to carry out this broad programme of testing very quickly, enabling him to publish a paper in Science as early as 1982. This paper would establish Prusiner as a key figure in research into scrapie and related diseases.

6.1. Testing for the involvement of protein

The basic idea of these experiments is quite simple; if you treat the scrapie agent with chemical detergents which can break or disrupt the amino-acid chains of protein, and if the results show that the activity of the agent has vanished, then you may logically conclude that proteins are a functional component of the agent. In biochemistry there are various chemical detergents and enzymes for denaturing

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[55] **Taubes, Gary** (1986) *op. cit.* note 6: 33
[56] **DeArmond, Stephen** (2000) Interview with author (UCSF, San Francisco: 17 August 2000)
[57] **Rhodes, Richard** (1997) *op. cit.* note 15: 163

proteins. The standard enzyme for denaturing proteins is protease-K. This enzyme is a non-specific protease, in other words, it can digest any amino-acid chain. Protease-K is a very effective enzyme for neutralising proteins. Prusiner aimed to test whether the scrapie agent involved proteins by using this detergent. The result was clear: when you put protease-K in the sample of scrapie, it lost its infectivity.

The second experiment involved chemical modification by diethyl pyrocarbonate (DEP). DEP also inactivates proteins by modifying proteins chemically. With DEP the scrapie agent was also inactivated. In addition, if the inactivated agent was treated with hydroxylamine, which reverses the chemical effect of DEP on protein, infectivity was restored. The third line of evidence is a treatment with a reagent, sodium dodecyl sulfate (SDS). SDS is a detergent widely used in experimental biology for solubilising membrane and protein assemblies. Particularly, this detergent disrupts most protein-protein interactions and lipid-protein interactions.[58] When the scrapie agent was exposed to this detergent, the infectivity was abolished. The fourth evidence that protein is an essential part of the agent involved exposure to chaotropic ions - another reagent that inactivates proteins. Low concentrations of the ions were shown to inactivate the agent. The fifth experimental result involved the use of phenol, a potent denaturant of protein. Phenol, in general, is useful to isolate nucleic acids, because it can remove proteins, while leaving nucleic acids intact. Again, with phenol, the agent was inactivated. The sixth biochemical experimental evidence involved exposure to urea, which is the soluble waste product of the breakdown of proteins and amino acids in mammals and other animals. It is also known to deactivate proteins. Prusiner and his team again observed that the scrapie agent lost its infectivity when exposed to urea.[59]

Prusiner went on to declare that "from all of these studies with chemical reagents that denature proteins but permit isolation of biologically active nucleic acids, we conclude that denaturation of a protein within the scrapie agent leads to inactivation of the infectious particles."[60] This means that scrapie infectivity depends on the

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[58] **Darnell, J., H. Lodish, D. Baltimore** (1986) *Molecular Cell Biology* (New York: Scientific American Books): 582-583.
[59] **Prusiner, Stanley** (1982a) *op. cit.* note 1
[60] *Ibid.*, 139

presence of an intact protein, which he locates within the scrapie agent – i.e. he assumes that the various protein denaturing agents he uses are acting on the agent itself, and not on some kind of agent-protein complex.

6.2. Testing for the involvement of nucleic acids

Prusiner's next step was to explore whether nucleic acids were involved in replication of the agent. From the conventional molecular biological view, all biological entities depend on nucleic acid-based genomes for their replication. Prusiner conducted a series of basic experiments to determine whether this was true in the case of scrapie agent. He treated the partially purified scrapie agent with a variety of nucleases - micrococcal nuclease, nuclease P, deoxyribonucleases I and II, ribonucleases A and T_1, and phosphodiesterases I and II – all of which break down nucleic acids and would be expected to lead to inactivation of the agent if a nucleic acid is involved in replication. Despite these attempts to inactivate the agent by means of nuclease treatment, he could not find any positive evidence of inactivation of the agent. The experimental phenomena could be explained by two possible interpretations. One was that nucleic acid was not involved in scrapie infectivity. On the other hand, as Prusiner mentioned in the paper, the same phenomena might be observed if the nucleic acids were protected by viral protein coats which the nucleases could not penetrate.[61]

Prusiner also invoked other experimental evidence to reinforce his preference for the former hypothesis – notably the radiobiological findings of Tikvah Alper, David Haig and Michael Clark, which had led them to conclude that the agent did not contain nucleic acids.[62] Prusiner also conducted similar experiments in collaboration with James Cleaver of the medical school in UCSF. Prusiner and Cleaver obtained a similar result to Alper's.[63]

Another experimental result that underpinned Prusiner's scepticism about nucleic acid was an experiment with psoralens. Psoralens are photo-sensitisers used for identifying DNA/RNA structures in cells and micro-organisms. Psoralens are known

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[61] *ibid.*, 140

[62] **Alper, T., W.A. Cramp, et al.** (1967) *op. cit.* note 24

[63] **Prusiner, Stanley** (1982a) *op. cit.* note 1: 140; **Prusiner, Stanley** (1984) *op. cit.* note 44: 53

to be able to pass through the protein coat of such organisms and reach nucleic acids. When exposed to UV light the psoralens then bind with the nucleic acid and inactivate it. According to Prusiner, psoralens have several advantages in searching for a nucleic acid genome: (1) low reactivity with proteins; (2) penetration of viral protein and lipid coats; and (3) formation of stable covalent linkages on photo-activation.[64] However, Prusiner found that exposure to psoralens produced no loss of scrapie infectivity. In addition, Prusiner exposed the scrapie agent to a number of other chemicals – zinc ions, and hydroxylamine – that were known to disrupt or modify nucleic acids. However, neither of these led to deactivation of the scrapie agent.

These experimental results were all consistent with the same conclusion as that reached by Tikvah Alper and her colleagues in 1967, i.e. that scrapie agent does not contain nucleic acid. However, Prusiner was very cautious when he came to draw conclusions from his own research. In particular, he was careful not to exclude other possible explanations for those experimental phenomena. He argued that his findings were consistent with two possible models of the replication of the scrapie agent. The first possibility was that the agent contained a nucleic acid, but that this nucleic acid-based genome was protected by a protein or lipo-protein coat. The second possible model Prusiner suggested was that the agent was devoid of nucleic acid. In this case, the protein component of the agent must somehow code for its own biosynthesis.[65] As Prusiner himself stated, this latter hypothesis "contradicted the 'central dogma' of molecular biology."[66] As we have seen, there are good reasons to suppose that Prusiner himself favoured this hypothesis. But he was too sensible to associate himself too closely with such a controversial view in a high profile publication. Consequently, in his 1982 Science which , he simply proposed the two alternative explanations of the data, adding that "there seems to be little advantage in championing one model over another."[67]

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[64] **Prusiner, Stanley** (1982a) *op. cit.* note 1: 140
[65] *Ibid.*, 142
[66] *Ibid.*, 142
[67] *Ibid.*, 142

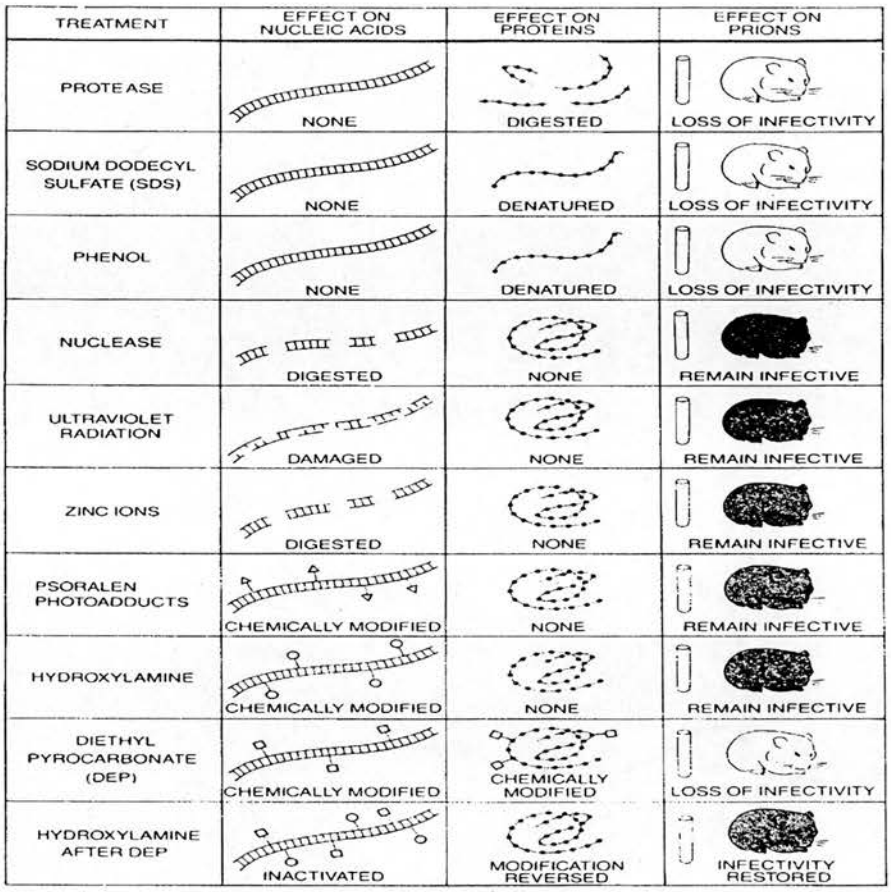

Figure 5: Examinations of chemical nature of the agent[68]

6.3. Prion: new name of the agent

While refusing to commit himself to controversial hypotheses about the absence of DNA in the scrapie agent, Prusiner did use his 1982 *Science* article to put forward some bold claims that would secure him considerable visibility in the field of scrapie research, and indeed in the field of infectious diseases more generally. For Prusiner, the scrapie agent was a novel infectious pathogen that could not be included in any conventional classification. In his article he states the difficulties in classifying of the agent, "rigid categorisation of the scrapie agent at this time would be premature."[69] But also argued that its biochemical and physical properties identified it as a "novel infectious entity". He claimed, "its [the scrapie agent] resistance to procedures that attack nucleic acids, its resistance to inactivation by heat, and its apparent small size

[68] **Prusiner, Stanley** (1984) *op. cit.* note 44: 54
[69] *Ibid.*, 142

all suggest that the scrapie agent is a novel infectious entity."[70] For the categorisation of this new pathogen, Prusiner suggested a new name for the agent.

Prusiner's decision to suggest a new name for the agent work reflected a wider sense among scrapie researchers that they were working on something peculiar and important. This is in turn apparent in a general interest in inventing a new classification for the agent. Between the late 1970s and early 1980s, several attempts were made to give the agent a proper name. In 1979, the Edinburgh-based researchers including Alan Dickinson, Richard Kimberlin and George Outram, suggested calling it a "virino", a name which suggests that it is related to viruses but that highlights its peculiarities, especially its small size.[71] Other scientists in the field called it a "slow (unconventional) virus". Prusiner and his team took the opportunity of their 1982 *Science* article to suggest a different name for the infectious agent which made no reference to any supposed viral characteristics, but instead pointed to particular biochemical properties of the agent. Stanley Prusiner suggested calling it "prion" [pronounced *pree-on*]. According to him, "prions are small proteinaceous infectious particles which are resistant to inactivation by most procedures that modify nucleic acids. The term "prion" underscores the requirement of a protein for infection; current knowledge does not allow exclusion of a small nucleic acid within the interior of the particle".[72] In this quotation, there is no specific definition of the prion – just a mention that proteins are a necessary component for infection.

When he planned to publish this paper and was thinking about what to call the agent, Prusiner and his team reviewed the first manuscript of the article and discussed the naming. One of his post-doctoral research fellows, David Bolton says, "as I recall, each of the internal reviewers had some comments and criticisms. Stan may or may not have altered the manuscript based on these. I do recall that the term 'prion' was chosen during that period, and that Paul Bendheim originally suggested the term 'prian' for proteinaceous infectious agent. Stan liked the basic idea but

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[70] *Ibid.*, 141

[71] **Dickinson, A. G., G. W. Outram** (1979) 'The scrapie replication-site hypothesis and its implications for pathogenesis', S. B. Prusiner and W. J. Hadlow (eds) *Slow Transmissible Diseases of the Nervous System* (London: Academic Press) **2:** 13-31

[72] **Prusiner, Stanley** (1982a) *op. cit. note 1*: 141

changed it to prion based on the similarity to subatomic particle names".[73] In an interview with science writer Gary Taubes in 1986, Prusiner said that, considering the way the word sounded, he had decided to transpose the "O" and the "I" in *pro*teinaceous *in*fectious particle, in order to make it more "terrific".[74]

It should be stressed that this new name served to set Prusiner apart from other researchers in two respects – first, in refusing to use terms including "unconventional slow virus" and "virino", and in avoiding any allusion to viruses in the name he chooses, Prusiner clearly distances himself from any supposition that the scrapie agent is necessarily similar to viruses. And secondly, in identifying prions as "small proteinaceous particles", he quite clearly stressed the essential role of proteins in the infectivity of the scrapie agent.

In his article in 1982, Prusiner did not say that prions consist solely of protein, i.e. he still did not rule out the possibility that nucleic acids are somehow involved in their replication. However, what he did do by calling them prions, and by thereby emphasising the functional importance of proteins in their action, was to play up the importance of his own research which had established that functional importance.

Another interesting feature of Prusiner's idea is that instead of putting forward a complete hypothesis about how the agent might replicate in the absence of a nucleic acid genome, or how it might account for other peculiar features of scrapie, he only provided a new name. At the time many scientists who were involved in scrapie research attempted to explain the perplexing characteristics of the disease with their own hypothetical ideas. Prusiner was more cautious and more astute. Acceptance of the term "prion" did not depend upon the truth of any complete theoretical speculations. Whatever the ultimate speculation of the nature of scrapie, the term prion could still serve to denote the causal agent.

7. Summary

In this chapter we have described how Prusiner began to be involved himself in scrapie research in the early 1970s. During the early years, he attempted to purify the

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[73] **Bolton, David** (2000) Personal communication (16 November 2000)
[74] **Taubes, Gary** (1986) *op. cit.* note 6: 30

agent by using the centrifugation method. The collaborative work with the RML researchers led him to achieve a partially purified form of the agent. Although this experimental project was regarded as a failed attempt to isolate the agent, he gained valuable experimental data and a valuable new technique for producing experimental material.

He then went on to develop a new faster and more economical bioassay technique with the hamster model of scrapie. This in turn enabled him to test the effects of a wide range of chemicals on his partially purified scrapie agent in a very short time, and to produce a considerable amount of biochemical data. On the basis of those experimental data Prusiner produced a high-profile publication in *Science* in 1982 in which he put forward some quite striking evidence for the involvement of protein in scrapie infectivity, and an equally striking failure to find evidence of the involvement of nucleic acids. This high profile publication also provided him with a platform from which to suggest that scrapie represents a new category of infectious agent for which he proposed the name "prion". He claimed that the precise nature of the infectious agent was not yet known, but it was characterised by precisely those phenomena that Prusiner had just demonstrated, namely the key role of protein and the lack of effect of biochemical reagents that would normally disrupt nucleic acids. As we will see in the next chapter, these claims not only established Prusiner's place on the map of scrapie research, but also precipitated a prolonged controversy over, and prompted further research into, the nature of these putative prions.

Chapter 8 - Prion controversy, 1982-1997

1. Years of Upheaval

1.1. Beginning of warfare

The publication of Stanley Prusiner's article in *Science* 1982[1] prompted immediate controversy among experienced scrapie researchers. As we have seen, Prusiner proposed two possible explanations for his results: firstly, that prions contained undetected nucleic acids; and secondly that prions were devoid of nucleic acids entirely. Although Prusiner did not rule out the first possibility, the research community was astonished that he could seriously propose that the agent might not contain nucleic acids. This was clearly an unorthodox approach, because it was a violation of Francis Crick's original "central dogma" of molecular biology, namely that biological information must be encoded in nucleic acid molecules.[2]

The first criticism came from a British scrapie researcher, Richard Kimberlin, in the Neuropathogenesis Unit (NPU) at Edinburgh. In a short paper in *Nature*,[3] Kimberlin pointed out that Prusiner's experimental evidence for the absence of an informational molecule in the agent could nonetheless be compatible with the existence of scrapie-specific nucleic acids. For instance, the failure of various reagents to inactivate the agent could be read as meaning that those reagents and enzymes had not gained access to the putative informational molecule.[4] Instead of using Prusiner's term "prion", Kimberlin thought that another neologism, "virino", previously suggested by his colleagues Alan Dickinson and George Outram, would be preferable for describing the possible character of protein-wrapped scrapie-specific nucleic acid. He also warned that scientists need not rush outside the bounds

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[1] **Prusiner, Stanley** (1982) 'Novel proteinaceous infectious particles cause scrapie', *Science 216* (9 April 1982): 136-144

[2] **Keyes, M. E.** (1999) 'The prion challenge to the 'central dogma' of molecular biology, 1965-1991: part II: the problem with prions', *Studies in History and Philosophy of Biological and Biomedical Sciences* 30(2): 186

[3] **Kimberlin, Richard H.** (1982) 'Scrapie agent: prions or virinos?', *Nature 297* (13 May 1982): 107-108

[4] *Ibid.*, 108

of conventional thinking in order to account for the behaviour of the scrapie agent.[5] A few weeks later, in an unsigned editorial in the *Lancet*,[6] Alan Dickinson stated that Prusiner's novel idea was premature as conventional viruses were wrongly thought by many people to be essentially protein in the 1930s. Furthermore, Prusiner's idea of the possible absence of a scrapie-specific genome could not account plausibly for the "various ramifications of the occurrence of different strains of scrapie."[7] In fact, these two papers were orchestrated reactions to Prusiner's argument. Kimberlin and Dickinson from NPU collectively agreed that Kimberlin should write the *Nature* article, and Dickinson should do the *Lancet* editorial without signing his name to it.[8]

Soon after their criticisms were published, Prusiner recognised the style of Dickinson's writing, and Dickinson "got a rocket", as he put it, from Prusiner.[9] It was published in the *Lancet* shortly afterwards.[10] In the letter, Prusiner expressed his scepticism about the Edinburgh group's twenty-year achievements, questioning the value of their work on the strain variation of the scrapie agent. He claimed in the letter "to suggest that isolation of a few strains of the scrapie agent in laboratory rodents for pathogenesis studies is an important achievement is questionable. These strains may describe a few biological characteristics of the scrapie agent, but they do not define or constrain the possible molecular structures of this unusual infectious particle."[11] This volatile confrontation was a sort of declaration of war against the Edinburgh group. When Prusiner criticised the existence of strain variations directly, he was crossing the Rubicon with regard to criticising the mainstream studies. His challenge was the first salvo of a long warfare between the prion-group and prion-sceptics.

Underlying the disagreement between Prusiner and the NPU researchers was a deeper divergence in their preferred methods and styles of investigation. This had already attracted comment from George Outram, one of Dickinson's colleagues in

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[5] *Ibid.*, 107

[6] **Anonymous Editorial** (1982) 'Scrapie: strategies, stalemates, and successes', *The Lancet* (29 May 1982): 1221-1223

[7] *Ibid.*, 1222

[8] **Dickinson, Alan G.** (1999) Interview with author (15 September 1999: Dunbar)

[9] *Ibid.*

[10] **Prusiner, Stanley B.** (1982) 'Research on scrapie', *Lancet* (28 August 1982): 494-495

NPU. He claimed that the prevailing experimental attitude was to use a mouse strain of the shortest incubation period; researchers would then proceed to apply every conceivable sophisticated procedure of modern biochemistry, immunology and molecular biology to it. However, he argued, "the danger with this approach is that in order to get meaningful answers the right questions must first be asked, [...] such a method would be the study of variation."[12] Outram's preferred approach was to focus more upon general biological phenomena, not upon a few molecular particulars.

The NPU group's achievements of the previous twenty years were generally appreciated by other groups of scientists. However, Prusiner's counter-claim in the letter to the *Lancet* shows no such appreciation of the preceding work. His main research priority was totally different from that of the mainstream researchers at the time: "elucidating the molecular structure was paramount for progress in this field",[13] he claimed. This was precisely the opposite direction from that chosen by others. This was a collision of different principles: the biological and the biochemical approach. One of the leading pathologists in NPU at Edinburgh, Hugh Fraser, said, "I was very critical [of Prusiner's idea]. I think I was critical because it was based on the ignorance of disease. It was based on unawareness, I would say ignorance, lack of awareness of our work!"[14] Another researcher in NPU, Moira Bruce, also felt upset when Prusiner ignored their achievements. She said, "he ignored whole, very well established series of observations about the strain variation. He ignored the most important bit of information, that of the nature of the agent from a biological perspective. I think we were very sceptical [about Prusiner's idea]. Plus, I think there was a bit of feeling that this was a sort of an upstart somebody had come into the field from nowhere, and who was he to tell us what the agent was. However, it wasn't just that. It was because the hypothesis just wasn't adequate for what we

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[11] *Ibid.*, 494

[12] **Outram, G. W.** (1980) 'Mouse scrapie: Black-box models and the slow encephalopathies', in F. C. Rose and P. O. Behan (eds) *Animal Models of Neurological Disease* (Bath: Pitman Medical): 360

[13] **Prusiner, Stanley B.** (1982) *op. cit.* note 10: 494

[14] **Fraser, Hugh** (1999) Interview with author (Edinburgh: 30 June 1999)

knew about the biology of the disease."[15] This difference between the prion group and the prion sceptics was clear. The philosophical gap between the groups would persist for two decades.

1.2. Mapping the battlefield

Soon after the exchange in *Nature* and *Lancet*, the battlelines were clearly drawn between Prusiner's group and the prion sceptics. The majority of scrapie researchers belonged to the sceptics' faction. Around the early 1980s, at least eight leading groups of scientists studied scrapie and its related disease.[16] It should be made clear here that the prion sceptics are not a homogeneous group or camp of scientists. Although they sometimes shared their main ideas on the nature of the agent, they sometimes took different positions. Thus, the term 'prion sceptics' means those who fundamentally disagreed with Prusiner's idea of a protein-only agent. The leading group of the sceptics was the Edinburgh group at NPU. Their experimental demonstration of strain variation was the most powerful scientific evidence to persuade others that the agent could be classified as virus-like. Most research camps appreciated the evidential strength of the Edinburgh group's work; due to variations of the agent, they believed that the agent must contain nucleic acid, even though its size and unusual properties seemed to indicate the opposite, i.e., that no nucleic acid was present. However, the prion sceptics sometimes put forward widely differing ideas on the nature of the agent. In a review paper by Richard Carp and his colleagues in 1985, though they agreed with Dickinson and Kimberlin's theory that the agent included nucleic acid, and disagreed with Prusiner's idea, they took a theoretical position called "the filamentous virus hypothesis".[17] At the time, seven

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[15] **Bruce, Moira E.** (1999) Interview with author (NPU, Edinburgh: 9 June 1999)

[16] The Neuropathogenesis Unit (NPU, Edinburgh), Heino Diringer's group in the Koch Institute (Berlin), Laura Manuelidis group in the Yale Medical School, Richard Carp's group in the Institute of Basic Research (IBR, New York), Gajdusek's group in the national institute of neurological disorders and stroke (NINDS, Bethesda), Richard Hadlow's group in the Rocky Mountain Laboratory (RML), Richard Marsh's group in the University of Wisconsin, Veterinary School (Madison), and Prusiner's group in UCSF.

[17] **Carp, R.H., P.A. Merz et al.** (1985) 'Nature of the scrapie agent: current status of facts and hypotheses', *Journal of General Virology 66*: 1357-1368

out of eight groups of scientists were critical of Prusiner's idea. In fact, Prusiner was isolated in the field of scrapie research.

Almost everyone involved with scrapie and its related diseases became Prusiner's adversaries. His new idea was considered "biological heresy". Moreover, other scientists dismissed his alleged prion theory as simply "a fairy tale." According to science writer Jennifer Cooke, "his many detractors at the time labelled Prusiner, and his heresy, as 'the P words'...he had created a new scientific word to fit a scientific entity that was still unknown. And for that he attracted a lot of publicity – a third 'P' word which resulted in grant money."[18] Even Prusiner's former collaborator, Richard Race, did not believe in his concept and its theoretical implication. He said, "it was heretical, this is nuts. It is crazy. But over the years my attitude is maybe it is, but we need better evidence."[19]

2. Dispute between the prion-group and prion-sceptics

2.1. Discovery of PrP, protease-resistant-protein

According to Richard Rhodes, Prusiner's decision to privilege the proteinaceous nature of the scrapie agent was a form of gambling – a risky game he would win only if further research into scrapie-related proteins proved fruitful.[20] The payoff spilled rapidly from his lab in the months that followed. One of his post-doctoral researchers, David Bolton, reported in *Science* that the purified scrapie protein had been found. [21] At the time, Prusiner's aim was to identify, isolate and purify the proteinaceous particles that he called prions, and that he plainly suspected might themselves be the agents of scrapie infection. He and his team had already managed to produce partially purified scrapie agent, but they were still looking for ways to

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[18] **Cooke, Jennifer** (1998) *Cannibals, cows and the CJD catastrophe* (Random House Australia: Sidney): 106

[19] **Race, Richard** (2000) Interview with author (RML, Hamilton, MT: 14 August 2000)

[20] **Rhodes, Richard** (1997) *Deadly Feast: Tracking the Secrets of a Terrifying New Plague*. (New York: Simon & Schuster): 162-164

[21] **Bolton, D. C., M. P. McKinley, et al.** (1982) 'Identification of a protein that purifies with the scrapie prion', *Science* *218*(4579): 1309-1311

improve on this.[22] Specifically, they now endeavoured to separate out the prion protein from the various hamster proteins that contaminated their scrapie material.

In 1982, Prusiner and his team decided to make use of the fact that the scrapie agent is known to be resistant to proteases. If samples of partially purified scrapie materials from infected hamster brains were treated with protease, most or all of the hamster proteins would be digested, leaving just the scrapie agent plus perhaps a few other hamster proteins intact.[23] By then comparing the digested brain material from scrapie-infected hamsters with similarly treated material from non-infected hamsters, it should be possible to identify those proteinaceous components that were unique to infected materials.

This work was undertaken by Frank Masiarz, who was the head of post-doctoral research in Prusiner's laboratory. However, his methods were not sufficiently discriminatory to reveal whether or not any intact proteins remained in the protease-digested hamster brain samples. In order to visualise such proteins, Masiarz first treated the undigested brain samples with a radiolabelling agent. After digestion with protease he then ran the preparation through a polychloride gel, which separates proteins chromatographically by molecular weight - if any intact proteins did indeed remain, it should then have been possible to identify them as distinct bands of radio-labelled material. However, Masiarz did not produce any results that he considered clear enough to be worth reporting. Only when Masiarz was about to leave the laboratory did he show Bolton, who decided to take over Masiarz's project, his notebooks. According to Bolton in his interview:

> when I went back through one of his notebooks, there was something that looked different between the scrapie sample and the normal sample. And it was sort of fuzzy band. So I asked him about it, and I said, you know this looks like you have got something here. And he said that no, that it wasn't really reproducible, and we had problems, it wasn't consistent between the things...Frank was pretty pessimistic. But when I looked at it, it looks to me very promising.[24]

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[22] It is notable that Prusiner increasingly called this partially purified scrapie preparation a "purified prion" preparation at the time.

[23] **Prusiner, Stanley** (1982) *op. cit.* note 1

[24] **Bolton, David** (2000a) Interview with author (31 July 2000: IBR, New York)

Bolton explained that the problem was very technical. Masiarz was labelling proteins with the Bolton-Hunter reagent, which is a particular kind of reagent that labels free-amino groups. The preparation of digested proteins contained so much such residual material that the background radioactivity practically obscured any remaining intact protein. Bolton said, "the problem was that most of the reagent, most of radioiodine doesn't get incorporated with the protein, but it stays in the solution. Thus when you look at the bottom of the gel, there's a tremendous background of non-specific radiation just from the reagent itself. This makes it very hard to see some of these things that are going on at the small molecular weight end."[25] However, Bolton was able to devise a way of separating out the intact protein from any residual labelling agent that might be getting in the way. He treated the protein preparations with sodium dodecylsulfate (SDS) and quinine hemisulfate to precipitate out the intact proteins. These could then be separated from the solution of labeled amino groups by centrifugation and washing with acetone. From this treatment, he could get much cleaner resolution in gels. When this separated material was run on a polychloride gel, a very clear band of protein showed up.

Having shown by this relatively crude means that it was possible to isolate intact proteins from scrapie-infected brain material after digestion with protease, Bolton then went on to perform a similar experiment, but using a much more precise method of differentiating the different protein components. He again treated scrapie infected and non-infected partially purified brain preparations with protease-K. He then separated out any remaining intact proteins by gel electrophoresis – a quite precise method for not only separating out different proteins, but for calculating their molecular weight by measuring how far they move along the gel. As in the previous experiment, some proteins in the scrapie-infected sample remained intact and showed up as a clear band on the electrophoresis gel. On the other hand, no protein was found in brain material from non-infected hamsters (see Figure 1). [26] Bolton

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[25] *Ibid.*

[26] **Bolton, D. C., M. P. McKinley, et al.** (1982) *op. cit.* note 21: 1310

concluded that the scrapie infected brain material contained a protease-resistant protein of molecular weight 27-30 K. Bolton called this PrP 27-30.[27]

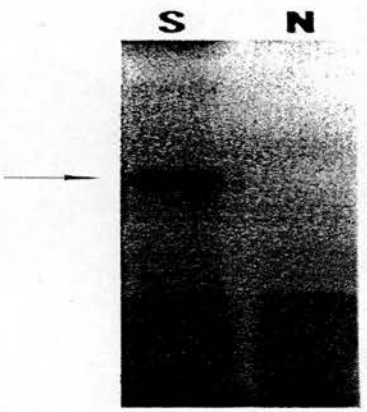

Figure 1: Protease-Resistant Protein (PrP) Radioiodinated and separated by SDS-Polyacrylamide Gel Electrophoresis.[28]

Bolton, like Prusiner, was cautious in drawing more general conclusions from this experiment, stating only that "since this protease K–resistant protein has not been found in purified fractions from normal hamster brains, we conclude that the protein is specifically associated with scrapie infection".[29] Notably, Bolton and Prusiner did not yet go so far as to say that it *is* the scrapie agent.

On the other hand, having identified PrP and discovered something of its properties, Prusiner and his team were now able to adapt this method to produce significant quantities of purified PrP. By taking samples from scrapie-infected hamster brains, digesting the proteins with proteases in the presence of SDS, spinning down and wash the precipitate, then running it through a polychloride gel to separate out the PrP, they were able to produce sufficient quantities of purified PrP on which to conduct further research. Moreover, this was a very quick procedure: the protein could be detected and quantified within one day after radiolabelling. Prusiner wrote that the implication of this finding was that the isolation of PrP represented a substantial decrease in the time required to gain information about the structure of the prion. Having a handle on one component of

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[27] **McKinley, M. P., D. C. Bolton, et al.** (1983) 'A protease-resistant protein is a structural component of the scrapie prion', *Cell* 35(1): 57

[28] *Ibid.*, 58

[29] **Bolton, D. C., M. P. McKinley, et al.** (1982) *op. cit.* note 21: 1310

the prion gave cause to hope that the discovery of any other components would follow in the not too distant future.[30] This became the basis of their next round of experiments

2.2. Prion protein gene (1985)

Having purified the protein PrP, Prusiner was now in a position to pursue further research into its role in scrapie infection. In particular, Prusiner was interested in testing his hypothesis that PrP was itself the agent, and that it propagated itself by catalysing its own manufacture in the cell. If that was the case, then it ought not to be possible to find any evidence that PrP was being manufactured by translation from either the host genome or a viral genome. If he could rule out genetic translation, this would place him in a much stronger position to suggest that the scrapie agent is a self-replicating protein. Consequently, he devised an experiment to test whether or not there was any evidence of PrP being manufactured by normal genetic means in infected hamster brains. For this work, Prusiner looked beyond the confines of the scrapie research community. He drew on the expertise of Leroy Hood of Caltech and Charles Weissmann of the University of Zurich. They were known amongst medical students as "gods of molecular biology".[31] Leroy Hood was a pioneer in cloning techniques for sequencing DNA. He was also one of the first advocates of, and a key player in, the Human Genome Project. Charles Weissmann is an expert in gene cloning and gene splicing. In 1980, he was the first scientist to make bacteria produce a facsimile of human interferon.[32] He was a founder of the Institute of Molecular Biology at Zurich in 1965. Weissmann accepted Prusiner's suggestion of

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[30] **Prusiner, S. B., D. F. Groth, et al.** (1985) 'Prions - structure, biology, and diseases', K. Maramorosch and J. J. McKelvey (eds) *Subviral Pathogens of Plants and Animals: Viroids and Prions* (New York: Academic Press): 369

[31] **Taubes, Gary** (1986) 'The game of the name is fame. But is it science?', *Discover* (December, 1986): 50

[32] **Lane, Neal F.** (1997) 'Double helixes and double-edged swords: cloning and the conundrum of scientific success', *National Press Club*
(22 April 1997: www.npf.gov.od/lpa/forum/lane/n1497/npc.htm)

collaboration, because he became fascinated with scrapie when he heard Prusiner's talk on the subject in Perth, Australia in 1982.[33]

Generally, molecular biological orthodoxy states that DNA sequences in the genes provide a template for the transcription of so-called complementary DNA (cDNA). This in turn provides a template for transcribing messenger RNA (mRNA). And the messenger RNA in turn provides a template for reading off the sequence of amino acids that make up a protein. Prusiner's aim was to see if it is possible to identify any polynucleotides in scrapie-infected brain material that might correspond to these stages in the manufacture of PrP. This was a complex process that involved a number of experimental steps.

First, in 1984, the Hood and Prusiner team successfully produced a number of fairly short amino acid chains, oligopeptides, from PrP.[34] These were particular sequences of amino-acids which, taken together, would almost certainly be unique to PrP. Knowing these amino-acid sequence, they were then able to work backwards to specify what nucleotide sequences in mRNA would code for these.[35] However, the problem was that there is redundancy in the coding, i.e. most amino acids can be coded by more than one nucleotide sequence. Consequently, working backwards from oligopeptides to nucleotide sequences leads to the specification of a rather large number of mRNA sequences, each of which could code for the respective oligopeptide chains of PrP. Prusiner undertook the rather laborious task of chemically manufacturing all of these different candidate oligonucleotide sequences so-called icosamers (i.e. functionally equivalent structural variants). Prusiner needed to find out if any of these candidate mRNA sequences were identical to mRNA that actually occurs in cells where scrapie is replicating and hence where PrP is being manufactured. If he *could* find such mRNA *in vivo*, then it would show that PrP is synthesised from genetic information, and would refute his self-replicating protein hypothesis.

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[33] **Brown, Phyllida** (1999) 'Charles Weissmann: another new challenge', *Current Biology* 9(17): R625

[34] **Prusiner, S. B., D.F. Groth, et al.** (1984) 'Purification and structural studies of a major scrapie prion protein', *Cell* 38: 127-134

[35] *Ibid.*, 132

In order to start looking for this mRNA in scrapie-infected cells, Prusiner had meanwhile initiated another set of procedures. He inoculated hamsters with scrapie. Some time later, when he judged that scrapie replication, and by implication PrP production, would be proceeding at a maximum rate, he removed and homogenised their brains. He now extracted mRNA from this brain material, using a standard biochemical procedure. This mRNA would include polycleotides coding for *all* proteins that were currently being produced. If PrP production depends upon a PrP-specific mRNA, then this should be included in the mixture. Using molecular biological cloning techniques, Prusiner used this mixed mRNA to produce an equally mixed preparation of cDNA. Again, if PrP is coded by a gene, then this cDNA mixture should include PrP-specific cDNA.

This cDNA was then transferred into *E.coli.* This involved a fairly random procedure, in which a culture of *E.coli* was bathed in a solution of the cDNA, and some of the *E.coli* bacteria picked up some of the bits of cDNA and incorporated them into their own genomes. The bacteria were then plated out and grown on agar, so that individual bacteria grew into distinct colonies which could in turn be cultured on separate plates. By this means, Prusiner produced what he called a gene "library" of *E.coli* cultures, each of which might include in its genome one or more of the cDNA strands prepared from the mRNA from scrapie-infected hamsters. If there exists a PrP-specific cDNA, then some of these *E.coli* cultures should contain it. However, this library was not catalogued, i.e. Prusiner had no prior way of knowing which if any of the *E.coli* cultures contained which of the many kinds of cDNA he had extracted from the hamster cells. Rather, his "library" was just a random selection of cDNA-carriers. [36]

The next step was that Prusiner's team had to find out if any of the candidate PrP-specific mRNA sequences that they had manufactured corresponded to the hamster-derived cDNA in any of the *E.coli* cultures that made up this "gene library". For this purpose, Prusiner cloned radioactively labelled mRNA from each of his candidate PrP-specific mRNA preparations. He then mixed each of these mRNA samples with

[36] Specifically, it is not a print library of sequenced genes, of the kind later written by the Human Genome Project.

samples from each E.coli culture in his hamster cDNA library. If any of the mRNA preparations was complementary to any of the hamster cDNA incorporated into the *E.coli* genome, then the labelled mRNA would bind with the respective *E.coli* culture.

As a result of this screening procedure, Prusiner found that some of his PrP-specific mRNA did indeed bind to the *E.coli* genome in some of his cultures, i.e. these mRNA sequences were indeed complementary to cDNA derived from scrapie infected hamsters. Contrary to what he expected, Prusiner had demonstrated that PrP was manufactured in scrapie-infected hamster cells by a process of translation from information coded in a nucleic acid genome. Moreover, he had now cultured and identified a strain of *E.coli* that actually carried the relevant stretch of genome (or rather the cDNA that was the first transcription product of that genome).

It should be noted, though, that at this stage Prusiner still did not know exactly where this cDNA originated from in scrapie-infected hamster cells. It might be transcribed from the hamster's own genome, or it might be transcribed from an exogenous genome, e.g. one belonging to a putative scrapie virus. Thus, he needed to do a further series of experiments to identify which genome it originated in. From the strain *E.coli* carrying the relevant piece of cDNA, Prusiner's team were in turn able to prepare a cDNA probe, i.e. a preparation of cloned and marked cDNA, that they could use to look for related genomic material in other preparations. Prusiner used this cloned cDNA probe to look for PrP-specific nucleic acid sequences in centrifugally purified preparations of scrapie agent, i.e. his "purified prion" preparations. He was unable to find any such material. This implied that PrP is not encoded by a nucleic acid genome present in the agent itself. Prusiner took this as further proof against the suggestion that the scrapie agent is a virus. However, when Prusiner used his cloned cDNA probe to examine the hamster genome, he found that it was indeed complementary to a section of DNA in the genome itself, i.e. they had now identified a hamster gene that codes for PrP. Moreover, they showed that this gene is present in non-infected as well as infected hamster cells, i.e. it is a part of the normal hamster genome.[37]

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[37] **Oesch, B., D. Westaway, et al.** (1985) 'A cellular gene encodes scrapie PrP 27-30 protein', *Cell* **40**: 735-746

All this of course constituted strong evidence against Prusiner's original theory that the scrapie agent is a self-replicating protein, since he had shown that PrP, the protein he considered most likely to play this role, was a product of the hamster's own genes. Prusiner and his colleagues took six months to make sense of this "self-inflicted apparent disproof of his theory".[38] Bolton, a Prusiner researcher at that time, says, "the impression I get is that they were quite perplexed about this gene showing up. If you read the articles, Weissmann seems uncomfortable with how you mesh this being a normal gene with it being a prion."[39]

If this work effectively refuted Prusiner's self-replicating protein hypothesis, however, it did raise further interesting questions about PrP. Specifically, if the PrP gene is present in both non-infected and infected hamster cells, why does the PrP protein only show up in the latter? In other words, there still appeared to be some association between PrP and scrapie infection, and Prusiner now wanted to know what this might be. Consequently, Prusiner's next experiment involved looking to see if a different technique from that used by Bolton to isolate PrP from infected cells might indicate that it is only present in non-infected cells. For this, he used an immunological technique. He produced marked antisera which would bind to and reveal the presence of PrP. When he used these antisera on extracts from non-infected brain, they bound to a protein. This technique thus indicated that a molecule immunologically identical to PrP occurs also in non-infected hamsters.[40] However, when the same immunological marker was used on extracts of non-infected hamster brain that had been treated with protease-K, it failed to bind to anything. This indicated that whereas PrP from scrapie-infected brain is resistant to digestion by protease, the immunologically identical molecule from non-infected brain is *not* resistant.[41] Prusiner regarded this as highly suggestive – specifically, it suggested that the PrP gene codes for a protein that can exist in two different forms, one of which occurs in non-infected cells and is susceptible to protease digestion, and another that

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[38] **Taubes, Gary** (1986) *op. cit.* note 31: 50

[39] **Bolton, David** (2000a) Interview with author (31 July 2000: IBR, New York)

[40] **Bendheim, P.E., Barry, R.A., et al.** (1984) 'Antibodies to a scrapie prion protein' *Nature* 310 (2 August 1984): 418-421; **Barry, R.A., Mckinley, M.P., et al.** (1985) 'Antibodies to the scrapie protein decorate prion rods' *The Journal of Immunology 135* (1): 603-613

[41] **Oesch, B., D. Westaway, et al.** (1985) *op. cit.* note 37

occurs in infected cells and is protease-resistant. Since both proteins were presumably coded by the same gene and were immunologically identical, Prusiner and his team supposed that they must comprise identical amino-acid sequences. Consequently, he cautiously hypothesised that their different chemical properties must be due to post-translation differences in molecular conformation, i.e. to difference in the way the protein chain was folded that were not determined by genetic information.[42]

Around 1986, Prusiner also changed what PrP stands for, from protease-resistant protein, i.e. the form specifically found in infected cells, to prion protein, encompassing both forms of the protein coded by the PrP gene. At the same time, he introduced the new terminology PrP^{C} and PrP^{Sc} to distinguish what he now called "cellular and scrapie prion proteins".

In conclusion, Prusiner's experimental results effectively disapproved Prusiner's own initial hypothesis that the scrapie agent is simply a self-replicating protein associated with and perhaps even identical with PrP. However, he has nonetheless managed to salvage something of his protein hypothesis by raising further interesting questions about the role of PrP in scrapie infection. Although the prion protein gene produces both the normal and pathological forms of the protein, Prusiner and Weissmann suggested after long speculation that the protease-resistant, disease-associated from of PrP was responsible for scrapie-like diseases. And while he might not yet have been in position to formulate this view explicitly, it appears that he was already entertaining a suspicion that infection might proceed through the conversion of PrP^{C} into more PrP^{Sc}.[43]

2.3. Is prion protein infectious? Counter-evidence (1986-1990)

Despite Prusiner's impressive technical accomplishments in identifying and isolating PrP and the gene that coded for it, other scientists remained sceptical about the theoretical conclusions he drew from his work, and specifically about his claims

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[42] **Meyer, P.K., M.P. McKinley et al.** (1986) 'Separation and properties of cellular and scrapie prion proteins', *PNAS 83*: 2310-2314

[43] **Prusiner, S. B., M. Scott, et al.** (1990) 'Transgenetic studies implicate interactions between homologous PrP isoform in scrapie prion replication', *Cell 63* (16 November 1990): 673-685

that PrP was a key factor in scrapie infectivity. Furthermore, prion-sceptical scientists continued to conduct research that appears to support their scepticism.

At the same time as Prusiner was pursuing the PrP gene, a group of scrapie researchers in the Rocky Mountain Laboratory (RML), led by Bruce Chesebro, launched a similar project to scrutinise the troublesome protein, including finding a gene that codes for PrP in mice. The RML had good facilities for experimentation with molecular biology, and they found the same gene in mice.[44] The experimental process was nearly the same as what Prusiner's team did with Weissmann. With the same small amino acid sequences from scrapie protein that were isolated by Prusiner and Hood's team in 1984, Chesebro's team synthesised a mixture of oligonucleotides for use as a hybridisation probe to analyse mRNA populations derived from infected and uninfected animals. As a result of this investigation, like Prusiner, they concluded that the gene for the normal and pathological proteins was identical, and there was no evidence for any unique messenger RNA (mRNA) associated with scrapie infectivity. And like Prusiner, they drew possible implications from this finding. Firstly, it could be seen as evidence against the view that scrapie-specific is responsible for the infectivity of scrapie. Secondly, if expression of this protein is associated with scrapie, then Chesebro and his team speculated that it could be a post-transcriptional or a mutational modification.[45]

More interestingly, Chesebro's team failed to find any PrP-specific mRNA in mouse spleen. The PrP-specific mRNA appeared only in scrapie-affected brain, not in the spleen or in the liver at all. According to many pathogenetic studies of scrapie, the agent was known to replicate initially in spleen.[46] If PrP is really the infective agent, why was PrP-related mRNA not found in spleen? Chesebro concluded that PrP 27-30, which was the candidate infectious agent for Prusiner's group, might not

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[44] **Chesebro, B., R. Race, et al.** (1985) 'Identification of scrapie prion protein-specific mRNA in scrapie-infected and uninfected brain', *Nature* ***315***(23 May 1985): 313-333

[45] *Ibid.*, 332

[46] **Kimberlin, R. H.** (1979) 'Early events in the pathogenesis of scrapie in mice: biological and biochemical studies', S. B. Prusiner and W. J. Hadlow (eds) *Slow Transmissible Diseases of the Nervous System* (New York: Academic Press) **2:** 33-54; **Outram, G. W.** (1976) 'The pathogenesis of scrapie in mice', in R. H. Kimberlin (ed.) *Slow Virus Diseases of Animals and Man* (Amsterdam: North-Holland Publishing Co.): 325-357

be specific for the infectious scrapie agent.[47] This experimental result cast doubt on Prusiner's observation in 1985.

Shortly afterwards, Laura Manuelidis at the Yale Medical School – a worldwide CJD expert, came up with an interesting experimental result showing that the prion protein might not be linked to the infectivity of scrapie.[48] Manuelidis' team set out to reassess the effect of treatment with protease-K on scrapie infectivity. Other researchers had already shown that protease-K significantly reduced scrapie infectivity,[49] whereas Prusiner's claims rested on the assumption that the infectious agent resists protease-K treatment. Manuelidis now showed that protease treatment of CJD brain material does indeed produce a protease-K resistant form of PrP as Prusiner's team observed. But at the same time, Manuelidis also observed that this treatment reduces infectivity by more than 90%.[50] Furthermore, she found that in CJD preparations, the major protein equivalent to PrP 27-30 in Prusiner's experiment, could be separated from infectivity under mild non-denaturing conditions, while Prusiner's group suggested that the infectivity was inseparable from PrP.[51] Also, Manuelidis and her colleagues later reported that when they attempted to separate different molecules from the infected brain samples, they found that the most infectious part was not PrP but a fraction containing other proteins and nucleic acids.[52] These studies suggested that PrP in itself is unlikely to be the replicating component of the infectious agent. Instead, she claimed that the agent was like a virus and had its own informational molecule. Many viruses, she said, are hardy and even resist treatment with enzymes that digest genetic material. These viruses like the polioviruses are packed inside a protein shell that protects them. "Think of all the

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[47] **Chesebro, B., R. Race, et al.** (1985) *op. cit.* note 44: 332

[48] **Manuelidis, L., T. Sklaviadis, et al.** (1987) 'Evidence suggesting that PrP is not the infectious agent in Creutzfeldt-Jakob disease', *EMBO Journal* 6(2): 341-347

[49] **Millson, G. C., G. D. Hunter, et al.** (1976) 'The physico-chemical nature of the scrapie agent', R. H. Kimberlin (ed.) *Slow Virus Diseases of Animals and Man* (Oxford: North-Holland Publishing Co.): 243-266; **Lax, A.J., Millson, G.C., Manning, E.J.** (1983) "Involvement of protein in scrapie agent infectivity' *Research in Veterinary Science 34*: 155-158

[50] **Manuelidis, L., Valley, S., Manuelidis, E.E.** (1985) 'Specific proteins associated with Creutzfeldt-Jakob disease and scrapie share antigenic and carbohydrate determinants' *PNAS 82*: 4263-4267

[51] **Manuelidis, L., T. Sklaviadis, et al.** (1987) *op. cit.* note 48: 345

viruses out there that have to get through the gastrointestinal tract," she said, "they have to deal with all sorts of lousy environments."[53]

Also in 1989, more good news for the sceptics came from Edinburgh. Richard Kimberlin reported his experimental results. As other Edinburgh researchers had done, he had based his experiments on the biological measurement of incubation time and pathological changes.[54] Prion sceptics continued to point out that Prusiner's suggestion that the scrapie agent is an infectious protein seems to be incapable of accounting for the significant and problematic fact of strain variation in scrapie, which implies that the scrapie agent must possess its own genome. This objection was reinforced when Kimberlin and his colleagues published new work on strain variation. Kimberlin and his colleagues studied the transmission of different strains of scrapie from mice to hamsters and then back to mice. In this experiment, each strain of the agent maintained its distinctive pathogenic identity when the agent was transferred between different species like mice and hamsters. Kimberlin claimed that, in spite of the species barrier, the scrapie agent maintains its genomic character when it jumps to another species. From this experiment, Kimberlin speculated that "it is likely that the scrapie genome is a very small 'regulatory' nucleic acid which may not code for protein (hence the need for a 'protective' host-coded protein such as PrP). A major criterion for recognising candidate genomes is that there should be sequence differences according to the strain of agent."[55] In other words, while the scrapie agent may rely on the host genome to manufacture its protein constituents, the strain is not decided by the gene of the animal that is infected, but is carried by the infective agent.[56] This was at odds with Prusiner's hypothesis that the scrapie agent is simply a protein coded by the host genome, and further reinforced the view that the agent

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[52] **Sklaviadis, T.K., L. Manuelidis, E. E. Manuelidis** (1989) 'Physical properties of the Creutzfeldt-Jakob disease agent', *Journal of Virology63* (3): 1212-1222

[53] **Kolata, Gina** (1994) 'Viruses or prions, an old medical debate still rages', *New York Times* (4 October 1994)

[54] **Kimberlin, R. H., C.A. Walker, et al.** (1989) 'The genomic identity of different strains of mouse scrapie is expressed in hamsters and preserved on reisolation in mice', *Journal of General Virology* **70**: 2017-2025

[55] *Ibid.*, 2018

[56] **Dealler, S.** (1996) *Lethal Legacy: BSE-Search for the Truth* (London: Bloomsbury): 52

must have a genome of its own. Indeed, Kimberlin actually included the phrase "genomic identity" in the title of his 1989 paper.

As a result of these experimental results, the prion sceptics remained unconvinced, and could point both to Prusiner's failure to link PrP unequivocally to infectivity, and to his failure to account for strain variation and its conservation when transferred across different species. Meanwhile, as more and more energy and resources were invested in scrapie research, the stakes grew higher, and between 1986 and 1989, the scrapie research community was embroiled in their most bitter clashes in the history of the prion controversy. Each camp presented their experimental achievements to refute their opponents. However, the dispute was moving beyond a rational debate. Throughout these experimental exchanges, the relations between the two sides were becoming increasingly acrimonious. For instance, at the CIBA Foundation meeting in 1988, there was a major confrontation and the controversy between the prion group and prion sceptics was intensified. It was too intense to make a transcript of the dialogue, so the meeting organisers stopped recording and turned off the microphone. George Carlson says, "I was amazed, I never saw anything like that. The personalities were amazing. You had people yelling at each other at meetings...I mean it is mind-boggling, absolutely mind-boggling. The animosity between groups, it was very controversial."[57]

2.4. Transgenic experiments (1989-1991)

Meanwhile, Prusiner's lab in San Francisco launched an ambitious series of experiments adopting yet another set of new experimental techniques from the cutting edge of molecular biology, namely the construction of transgenic organisms, which he intended to further elucidate the role of PrP and its gene in scrapie and other diseases. The project was led by a Scottish molecular biologist, Mike Scott, and a new postdoctoral researcher, Karen Hsiao. During his search for the hamster PrP gene, Prusiner's team had developed techniques for cloning the cDNA complementary to that gene. It was a small step to being able to produce and clone the gene itself. Moreover, techniques had recently become available for inserting

such cloned genes into the embryos of various organisms including mice.[58] Consequently, Prusiner's team were now able to create a strain of transgenic mice that carried the hamster PrP gene.[59] The transgenic mice were created by injecting the PrP gene into the male pronucleus of a fertilised mouse egg. The injected eggs were then transferred into pseudopregnant mice. According to Jean Manson and Nadia Tuzi, "this approach generates transgenic mice in which the transgene is integrated randomly into the murine genome. Although the expression level and distribution of PrP cannot be controlled with this transgenic approach, its use has yielded many interesting and informative TSE models."[60]

This elegant method provided a powerful means of developing whole-animal models to study the function of specific genes and the proteins they encode. In Prusiner's lab, they now used this transgenic mouse to investigate the species specificity of particular strains of scrapie.[61] When Prusiner inoculated ordinary mice with purified scrapie agent of a strain that had been continuously passaged through hamsters, it took 500 days for symptoms to manifest themselves. However, when he inoculated the same hamster-passaged scrapie agent into the transgenic mice carrying the hamster PrP gene, the incubation time is reduced by 140 days on

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[57] **Carlson, George** (2000) Interview with author (9 August 2000: the Mclaughlin Research Institute, Great Falls, Montana)

[58] The method developed rapidly during the 1980s. According to a historian of molecular biology, Michel Morange, the technique ushered in the age of contemporary molecular biology. [**Morange, Michel** (1998) *A history of molecular biology* (Cambridge: Harvard University Press)]

[59] This method was devised in 1973 by two researchers, F. Graham and A. Van Der Erb. [**Graham, F.L. and A.J. Van der Erb** (1973) 'A new technique for the assay of infectivity of Human Adenovirus DNA', *Virology 52*: 456-467] However, the main progress of transgenic technique developed with the creation of transgenic animals in 1980. A Yale biologist, Frank Ruddle, injected mouse embryos a few hours old with foreign DNA that then integrated into their chromosomes. [**Gordon, J.W., G.A. Scangos, et al.**(1980) 'Generic transformation of mouse embryos by mocroinjection of purified DNA', *PNAS 77*: 7380-7384] After several rounds of cell division in vitro, the embryos were implanted into surrogate mothers, which twenty days later, gave birth to a total of seventy-eight pups, two of which had integrated the foreign DNA into most of their cells. [**Morange, Michel** (1998) *op. cit.* note 58: 202]

[60] **Manson, J.C. and N.L. Tuzi** (2001) 'Transgenic models of the transmissible spongiform encephalopathies', *Expert Reviews in Molecular Medicine* (11 May, 2001: www-ermm.cbcu.cam.ac.uk/01002952h.htm): 3

[61] **Sofroniew, M. V. and K. Staley** (1991) 'Transgenic modelling of neurodegenerative events gathers momentum', *Trends in Neuroscience* ***14***(12): 513

average and then remained constant.[62] Prusiner and his supporters interpret this in terms of their theory that the scrapie agent is a variant form of PrP that catalyses its own production from ordinary PrP. Specifically, they supposed that there are genetically determined differences between hamster and mouse PrP, and that hamster PrP^{Sc} will more readily convert hamster PrP^{C} than mouse PrP^{C}. If that was the case, it might be expected that incubation of hamster-passaged scrapie would be quicker in mice that carried hamster PrP genes, and consequently manufactured hamster PrP protein, than in mice that did not. This was indeed the result that Prusiner and his team produced, and they took this as evidence in support of the prion theory. From Prusiner's point of view, the transgenic mice indicated that hamster PrP^{Sc} in the inoculum was the sole cause of the disease, and that it acts as a template for the conversion of the hamster PrP^{C} ($HaPrP^{C}$) protein in the transgenic mouse into more $HaPrP^{Sc}$.[63] As Charles Weissmann pointed out, within the framework of the "protein-only" hypothesis, these results were significant in showing that hamster-derived prion more readily converts the transgenic hamster PrP^{C} than endogenous murine PrP^{C} into the PrP^{Sc} form.[64]

Another significant experimental outcome was also reported by one of Prusiner's post-doctoral fellows, Karen Hsiao. She had for some time had an interest in Gerstmann-Straussler-Scheinker (GSS) syndrome, a rare inherited CJD-like human neurodegenerative disease that Gajdusek suggested in 1981 might also belong in the category of scrapie-like slow virus diseases. [65] Hsiao sequenced the PrP gene from GSS cases and found that it carries a mutation, i.e. it codes for a variant of the PrP

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[62] **Prusiner, S. B., M. Scott, et al.** (1990) 'Transgenetic studies implicate interactions between homologous PrP isoform in scrapie prion replication', *Cell* ***63*** (16 November 1990): 673-685

[63] **Hunter, N.** (1991) "Scrapie and GSS--the importance of protein" *Trends in Neurosciences* ***14***(9): 389

[64] **Weissmann, C.** (1991) 'Spongiform encephalopathies: the prion's progress', *Nature* ***349***(6310): 570

[65] GSS is one of the TSE diseases in humans. In 1936, two neurologists, Gerstmann and Straussler, and a neuropathologist, Scheinker, first described a family with unusual neurodegenerative symptoms. It is an extremely rare disease. This strikes only one in about 10 to 100 million people. Some of its pathological features resemble those of Alzheimer's disease. [**Masters, C.L., D.C. Gajdusek, C.J. Gibbs** (1981) 'Creutzfeldt-Jakob disease virus isolation from the Gerstmann-Straussler syndrome', *Brain 104*: 559-558]

protein.[66] She observed that one of the DNA sequences in the human prion gene was mutated from proline to leucine at position 102, and speculated that this was the cause of the rare inherited disease, GSS.[67] Hsiao constructed a transgenic mouse containing the GSS prion gene (GSS PrP) that harboured the same mutation. The mutated transgenic mouse died from spongiform neurological disease at around 166 days without prior exposure to scrapie or GSS. This means that the transgenic mice developed neurodegenerative symptoms spontaneously. This spontaneous disease in the transgenic mice suggested strongly that the disease was indeed caused by a variant form of PrP, in this case one that was actually coded by the PrP gene. Prusiner and Hsiao suggested that GSS is an "inherited prion disease".[68]

These transgenic experiments, and in particular Hsiao's GSS experiment, made a considerable impression on others both within the scientific community and more widely. A neurobiologist at Johns Hopkins University School of Medicine, Donald Price, said, "I think it's really extraordinary. A single mutation in a transgene, when put in a mouse, can cause clinical disease and brain pathology."[69] Many Prusiner supporters think that Hsiao's work provided vital data to persuade other scientists to believe the protein-only idea. In an interview, Stephen DeArmond, a neuropatholgist in Prusiner's camp, claimed that due to this experiment, the prion theory gained momentum:

> So, now indirect evidence for the protein-only hypothesis is building more and more. Momentum is gaining. So, now mutations, and then subsequently, all at about the same time, a number of laboratories show that mutations at different points accounted for other forms of CJD as well as other types of GSS-type disorders, and insertions occasionally did it also. So, again, the information is mounting.[70]

As he claimed, other scientists began to take an increasing interest in the possibility that other neurodegenerative disorders might have similar genetic basis,

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[66] **Hsiao, K. and S. B. Prusiner** (1990) 'Inherited human prion diseases', *Neurology* ***40***(12): 1820-7

[67] **Hsiao, K., H. F. Baker et al.** (1989) 'Linkage of the prion protein missense variant to Gersmann-Straussler Syndrome', *Nature 338*(6213): 342-345

[68] **Hsiao, K. and S. B. Prusiner** (1990) *op. cit.* note 66

[69] **Marx, J.** (1990) 'Human brain disease recreated in mice', *Science* ***250***(4987): 1509

[70] **DeArmond, Stephen** (2000) Interview with author (UCSF: 18 August 2000)

including fatal familial insomnia (FFI) that was currently classified as a prion disease.[71] Prusiner and his colleagues centred on these genetic diseases passionately. The transgenic experiments by Scott and Hsiao implied that the so-called prion diseases could be generated from genetic defects, not from virus-like infection. One of Weissmann's colleagues in Zurich, Adriano Aguzzi, summed up its positive implications. He says "the familial cases make it much more difficult to argue on the side of a virus. You can have close to 100% penetrance in these families - meaning if they have the mutation, they usually get the disease. So then you'd have to argue that there's some ubiquitous virus which infects everybody but will produce disease only in the patients who have the mutation. It's kind of acrobatics."[72]

In view of the attention and acclaim that this transgenic work was receiving, Prusiner now felt sufficiently confident to explicitly state the view that he had hitherto only hinted at, namely that prion is an infectious protein, without any nucleic acid component. From these encouraging experimental results, Prusiner formalised his idea of a protein-only agent. Since he suggested the novel concept of prion in 1982, he had never put forward the protein-only theory as his own preferred theoretical position for explaining his overall work. In 1991, however, he finally excluded the possibility of viral factor in the agent.[73] It was the first instance where he clearly talked about a prion as being protein only. He was now confident enough to claim the absence of any viral informational molecule from the agent. Prusiner thought he had enough data to exclude such a possibility.

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[71] Fatal Familial Insomnia (FFI) was first reported in 1982. This disease is similar to CJD, but shows more striking pathology; the thalamus, a large nucleus in the centre of the brain, was so markedly affected that it had collapsed and almost disappeared. The FFI patient has a sleep disturbance that rapidly progressed to a complete inability to sleep or to respond to most sleeping pills. [**Ridley, R. M. and H. F. Baker** (1998) *Fatal Protein: the story of CJD, BSE and other prion diseases*. (Oxford: Oxford University Press): 87] Interestingly, it is a family-based disease. In 1986, a neuropathologist, Pierluigi Gambetti, and his colleagues in the University Hospitals of Cleveland reported a large North Italian kindred having as many as 29 affected individuals among 288 family members spanning six generations. [**Lugaresi, E., R. Medori et al.** (1986) 'Fatal familial insomnia and dysautonomia with selective degeneration of thalamic nuclei', *New England Journal of Medicine 315*: 997-1003]; For a more detailed review on prion research into FFI, see **Aguzzi, A. and C. Weissmann** (1996) 'Sleepless in Bologna: transmission of fatal familial insomnia', *Trends in Microbiology* **4**(4): 129-31

[72] **Mestel, Rosie** (1996) 'Putting prions to the test', *Science 273* (5272): 187

[73] **Prusiner, S. B.** (1991) 'Molecular biology of prion diseases', *Science* 252(5012): 1515-22

This claim was now well received by many fellow scientists. Since Prusiner introduced his powerful transgenic technique to the field of scrapie research, his work gained more credit and publicity from many scientists and the general public. The changing public mood can be seen in some reactions of the mass media. In 1991, the *New York Times* reported Prusiner's transgenic work under the heading "heretical theory on brain diseases gains new ground".[74] Around the same time, there were also some positive responses from his fellow scientists. *Science* magazine reported Prusiner's achievements with transgenic mice, thereby supporting Prusiner's prion theory.[75] A molecular biologist in St. Mary's hospital in London, John Hardy, claimed that "this [Hsiao's] experiment should finally dispel the doubts of those who believed that a nucleic acid must be involved in the pathogenic process."[76]

The prion sceptics remained unconvinced, however. For one thing, they challenged the interpretation that the prion camp had placed on Hsiao's experiment. In particular, they were able to point out that the similarities between the neurodenerative disease suffered by Hsiao's transgenic GSS mice and transmissible diseases such as scrapie were limited. In scrapie, infection was characterised by the presence of a protease-resistant form of PrP. If the pathology of transgenic GSS PrP mice was similar to that caused by scrapie infection, it ought to be possible to isolate a similarly protease-resistant form of PrP from their brains. Hsiao and Prusiner had tried but failed to do so. Likewise, if GSS was indeed a prion disease, it ought to be possible to transmit that disease from transgenic GSS PrP mice to ordinary mice, but while Hsiao and Prusiner had attempted to do so, they failed. [77] Richard Carp, a leading prion sceptic, sees this as a serious flaw in the evidence, and stresses that "there has been a whole string of situations, where they transmit material, the Karin Hsiao mouse, where they had the 102 mutation, but if they put it into normal mice

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[74] **Blakeslee, Sandra** (1991) "Heretic theory on brain diseases gains new ground" *New York Times* (8 October, 1991): C12

[75] **Marx, J.** (1990) *op. cit.* note 69; **Marx, J.** (1991) 'Prion proposal proved?', *Science* **251**(4997): 1022-1023

[76] **Hardy, John** (1991) 'Prion dimers: a deadly duo?', *Trends in Neurosciences* 14 (10): 423

[77] **Hsiao, K. K., M. Scott, et al.** (1990) 'Spontaneous neurodegeneration in transgenic mice with mutant prion protein', *Science* **250**(4987): 1587-90

they get nothing. So, there has been no instance where artificially produced PrP has been infectious."[78]

The prion sceptics were not satisfied simply to point out gaps in Prusiner's aetiological arguments, however. In 1991, one of the prion sceptics at Edinburgh, Nora Hunter, published a paper outlining an alternative theory of the significance of PrP, which she argued provided a more adequate account of the theoretical evidence.[79] It was not necessary to regard the PrP protein as the infectious agent itself, or even as a component of the agent. Rather, the phenomena could be better explained if it was understood to be a receptor molecule, present in the host cells and involved in the process of infection by and replication of a scrapie virus, but not itself infectious. This idea of PrP protein as a receptor was underpinned by a recent study of the poliovirus receptor (PVR) protein,[80] which had shown that transgenic mice expressing human poliovirus receptor became susceptible to poliovirus. A similar theorisation of the PrP protein could account for much of what was shown about its involvement in scrapie infection.

Thus, where Prusiner had explained Scott's transgenic studies of cross-species infection in terms of the host genome coding for a version of the agent itself, the receptor molecule theory offered an alternative explanation. Strains of the disease passaged through a particular species might be expected to adapt to the particular version of the PrP protein receptor found in that species. The presence of hamster PrP in the transgenic mice would thus facilitate replication of the hamster scrapie virus, with the result that incubation would be quicker than in mice that did not possess hamster PrP. The receptor allows the hamster-passaged scrapie to infect transgenic mouse cells that are normally resistant because this hamster scrapie agent does not fit with the mouse PrP protein.[81]

This alternative view was supported by Hunter's allies. One of the American prion-sceptics, Robert Rohwer, an assistant professor of microbiology at the University of North Carolina at Chaple Hill, agreed with this view of the prion

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[78] **Carp, Richard** (2000) Interview with author (IBR, New York: 27 July 2000)

[79] **Hunter, N.** (1991) *op. cit.* note 63

[80] **Ren, R., F. Costantini et al.** (1990) 'Transgenic mice expressing a human poliovirus receptor: a new model for poliomyelitis', *Cell63* (2): 353-362

protein as a receptor. In an interview with the *New York Times* in 1991, he claimed that "in my view, this protein is a virus receptor that helps determine host susceptibility. The fact that there is only one protein and many strains of the disease implies there's got to be some nucleic acid somewhere."[82]

Meanwhile, in the case of Hsiao's transgenic GSS PrP theory, Hunter suggested that the pathology experienced by the transgenic PrP mice need not be attributed to the action of a variant form of PrP at all. Hunter pointed out that the transgenic GSS PrP mice carried more than 60 copies of the mutant PrP gene.[83] Consequently, without any detectable PrP in the sample and transmission, the neurodegeneration that occurred in these mice might simply be attributed to the fact that the mice were producing too much PrP, whereas Prusiner and Hsiao believed that one mutant caused the disease.

Whatever gaps there might be in Prusiner's aetiological arguments, and whatever room there might be for alternative explanations of the phenomena, however, Prusiner's transgenic work had at least succeeded in making PrP and its gene into one of the key foci of interest in research into scrapie and related diseases. The impact of Prusiner's transgenic experiments was enormous, and almost all research groups working in this field have since constructed their own transgenic models.

2.5. Unfinished war

Meanwhile, Prusiner was opening up another line of research into the role of PrP in scrapie and other diseases. Since Prusiner's team found two forms of prion protein, i.e., protease-soluble and resistant form, in 1985, he and his team had speculated about just how these two forms might differ from one another, and how an understanding of that difference might throw light on the processes of infection and pathogenesis. During the late 1980s, some researchers cautiously suggested that this might be only a matter of changes in the shape of the protein molecule. In general, genetic information determines the sequence of amino acid that make up the

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[81] *Ibid.*

[82] **Blakeslee, Sandra** (1991) "Heretic theory on brain diseases gains new ground" *New York Times* (8 October, 1991): C12

[83] **Hunter, N.** (1991) *op. cit.* note 63: 389

basic structure of a protein. After assembly this amino acid chain then folds itself into a stable shape or conformation. Prusiner and others speculated that the protease-soluble and –resistant forms of PrP might represent different conformations of the same basic molecule. They suspected that the process of infection, i.e. of transforming PrP^{C} into PrP^{Sc}, might be simply be a matter of switching between one conformation and another.[84]

In 1991, Prusiner began to collaborate with a young protein and pharmaceutical chemist, Fred Cohen, in UCSF. Cohen was an expert in the chemistry of protein folding. Prusiner and Cohen began to investigate chemical difference between the pathological form (PrP^{Sc}) and the normal form (PrP^{C}). Since Linus Pauling elucidated the general structures of proteins, particularly the helical form (known as α-helix) and sheet form (known as β-sheet), in the 1930s, techniques for studying protein structure had advanced enormously.[85] Fred Cohen and Prusiner now adopted another novel technique to analyse structure of the proteins: Fourier transform infrared (FTIR) Spectroscopy.[86]

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[84] **Oesch, B., D. Westaway, et al.** (1985) *op. cit.* note 37; **Chesebro, B., R. Race, et al.** (1985) *op. cit.* note 44; **Meyer, P.K., M.P. McKinley et al.** (1986) *op. cit.* note 42; **Caughey, B. B., A. Dong, et al.** (1991) 'Secondary structure analysis of the scrapie-associated protein PrP27-30 water by infrared spectroscopy', *Biochemistry* ***30***: 7672-7680

[85] Since Pauling's research into proteins in the 1930s, protein chemistry had progressed slowly. In 1972, Christian Anfinsen won the Nobel Prize in chemistry for his 1960 work at the NIH, which was a significant breakthrough in protein chemistry. His work showed that the final three-dimensional form of a protein is determined solely by its amino-acid sequence. During the 1970s and 1980s, many protein chemists have paid attention to the protein folding process. In the 1970s Michel Goldberg of the Pasteur Institute in Paris found that in many cases simple protein molecules clumped together into insoluble aggregates. This aggregate form of protein came to central stage protein chemistry in the 1980s. With regard to development of prion theory, the research progress of protein misfolding seems to be closely related. For more details on the review of the history of prion chemistry, particularly protein folding studies, see **Thomasson, W. A. B.** (2000) 'Unraveling the mystery of protein folding', *FASEB* (www.faseb.org/opar/protfold/protein.html); **Taubes, Gary** (1996) 'Misfolding the way to disease', *Science 271* (15 March 1996): 1493-1495

[86] FTIR spectroscopy is a quite new technology, exploits the fact that particular functional groups present in proteins, and especially highly polar bonds, resonate at around the frequency of infra-red light. This machine can record the interaction of infrared radiation with samples, measuring the frequencies at which the sample absorbs the radiation and the intensities of the absorption. Consequently, by studying the IR absorption spectra of protein molecules, it is possible to identify the presence of such bonds, and thereby to elucidate the structure of the molecule This technique was introduced to the field of scrapie research by researchers in RML in 1991. [For more detailed explanation of the FTIR, see **Griffith, P.R., J.A. de Haseth** (1986) *Fourier transform infrared spectrometry* (New York: John Wiley);

Using this technique, Cohen and Prusiner's team found that the normal prion protein was rich in α-helix but was devoid of β-sheet, whereas the pathological protein was high in β-sheet.[87] The team thus revealed a major morphological difference between the cellular isoform (normal form) and the scrapie isoform (pathological form). Cohen says in his interview, "the difference was a tremendous diminution in α-helical structure on going from the PrP^{C} isoform to the PrP^{Sc} isoform. And an even greater increase in β-structure going from the cellular isoform to the scrapie isoform. So here was one consequence, but two structures that were dramatically different."[88] This result confirmed that the difference was not derived from the DNA codes, but from conformational changes in the protein.

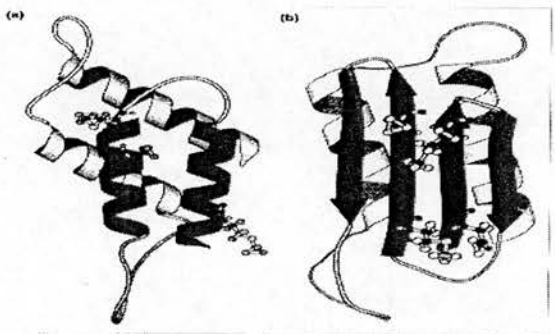

Figure 2: Two models of tertiary structures of PrP^{C} and PrP^{Sc}.[89] The left model is the normal PrP with helical structure (α-helix); the right model clearly shows its difference from the normal form of PrP. Some of α-helix structures are changed into β-sheet.

Meanwhile, Prusiner had a collaborative project with Weissmann to produce further evidence that they considered to support the conformation change theory. They had found a way of altering and thereby inactivating the PrP gene. Mice homozygous for the inactivated gene, called PrP-knockout mice, did not produce PrP. When these mice were inoculated with scrapie, they remained healthy for over a

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Caughey, B., R. Race et al. (1988) 'In vitro expression of cloned PrP cDNA derived from scrapie-infected mouse brain: lack of transmission of scrapie infectivity', *CIBA Foundation Symposium135: Novel Infectious Agents and the Central Nervous System: 197-208*]

[87] **Baldwin, M. A., K-M. Pan, et al.** (1994) 'Spectroscopic characterization of conformational differences between PrPc and PrPsc: an a-helix to b-sheet transition', *Philosophical Transactions of the Royal Society of London, Series B.* 343(29 Mar. 1994): 435

[88] **Cohen, Fred** (2000) Interview with author (UCSF, San Francisco: 22 August 2000)

[89] **Prusiner, S.B.** (1996) 'Molecular biology and pathogenesis of prion diseases', *Trends in Biological Science 21:* 483

year, whereas mice carrying the normal gene fell ill within around 120 days.[90] Prusiner argued that this showed that the scrapie prion could not propagate in the absence of the normal protein, a finding that he interpreted as supporting his view that propagation was a matter of conversion of normal into pathological PrP. Weissmann said, "the findings described in this paper in accordance with the 'protein-only' hypothesis and together with the large body of evidence amassed by Prusiner and his colleagues provide strong support for this model."[91]

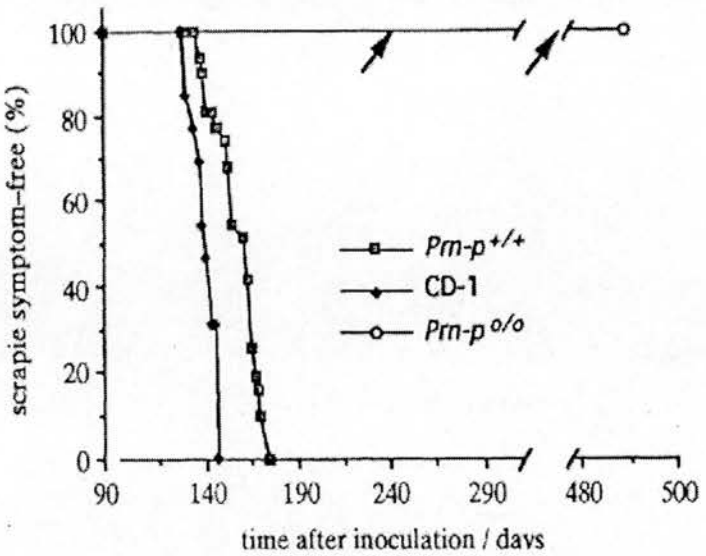

Figure 3: Scrapie resistance of mice with disrupted PrP genes $Prnp^{0/0}$ (PrP knockout) and $Prnp^{+/+}$(PrP containing) mice remaining symptoms-free at different times after inoculation with mouse scrapie prions.[92]

Weissmann and Prusiner's results were announced in September 1993, at a two-day meeting on prion diseases hosted by the Royal Society of London. At this meeting, Weissmann told an interviewer that "the weight of the evidence is quite heavily in favour of the prion hypothesis."[93] Not all those participating in the meeting would have agreed, however. At the same meeting, the troublesome issue of strain variation was again raised by a paper from the Edinburgh group. For the last three decades, the Edinburgh scientists had kept showing the existence of different

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[90] **Weissmann, C., H. Bueler, et al.** (1994) 'Susceptibility to scrapie in mice is dependent on PrP^{C}', *Philosophical Transactions of the Royal Society of London, Series B.* **343**(29 Mar. 1994): 431-434

[91] *Ibid.* 433

[92] **Weissmann, C., H. Bueler, et al.** (1994) *op. cit.* note 90: 432

[93] **Kingman, S.** (1993) 'London meeting explores the ins and outs of prions', *Science* **262:** 180.

strains with distinct incubation periods and pathological changes in brain. One of the leading scientists at NPU in Edinburgh, Moira Bruce, presented her work on transmission of BSE (Bovine Spongiform Encephalopathy), which was a newly found scrapie-like disease in cattle also known as "mad cow disease" in Britain. Bruce was working on BSE, which she had succeeded in transmitting into genetically homogeneous laboratory mice.[94] Seven different transmissions all showed identical lesion profiles, suggesting that the cattle housed only a single strain of the agent.[95] Moreover, cases of suspected BSE contracted from cattle had also been reported in domestic cats and in two zoo animals, a kudu and a nyala. Bruce succeeded in transmitting the disease from these cases into the same strain of mice. In all cases, the lesion profile was identical to that from BSE-infected cattle, but differed significantly from the lesion profile shown with two different strains of scrapie.

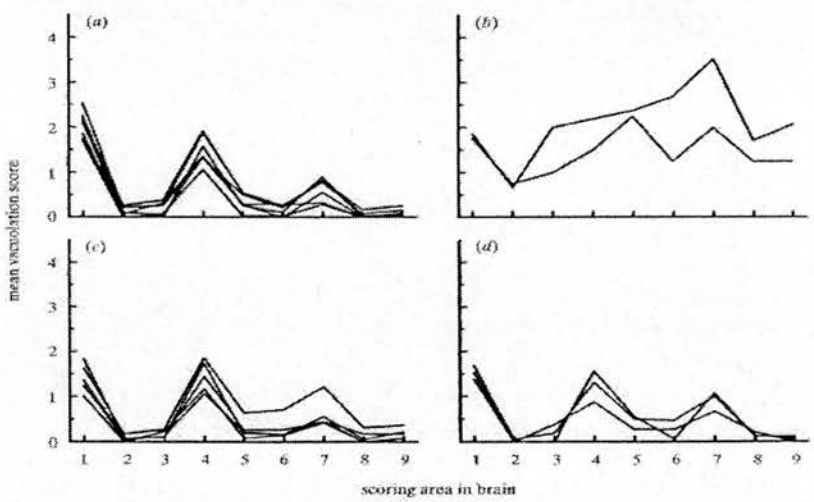

Figure 4: Pathological change (lesion profile) in RIII mice for (a) the seven BSE transmissions from cattle, (b) the two positive transmissions from natural sheep scrapie, (c) the transmissions from three cats, the kudu, and the nyala and (d) the transmissions from the experimentally BSE-infected sheep, goats and pigs.[96]

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[94] **Bruce, M., A. Chree, et al.** (1994) 'Transmission of bovine spongiform encephalopathy and scrapie to mice: strain variation and the species barrier', *Philosophical Transactions of the Royal Society, London, Series B, Biological Series* **343**: 405-411.

[95] The lesion profile was a tool to measure the quantified variation in the pathology, and was introduced by a neuropathologist in NPU, Hugh Fraser, in the early 1960s. [**Fraser, H. and A. G. Dickinson** (1968) 'The sequential development of the brain lesions of scrapie in three strains of mice', *Journal of Comparative Pathology* **78**: 301-311] More detailed explanation of this method is available in chapter 3.

[96] *Ibid.*, 407

Bruce took these as confirming that the cats, kudu and nyala were indeed infected with BSE rather than scrapie or some other diseases. More importantly, she also argued that these results, like Kimberlin's earlier study of scrapie transmission from hamsters to mice and back, indicated that the BSE agent must possess its own genome. If, as Prusiner and his supporters argued, prion diseases were transmitted solely by conformational change in the host PrP protein, then a disease such as BSE should not retain its distinctive character as it was transmitted from one species to another. That BSE had in fact conserved its distinct character as it was transmitted from cattle through several different species and into mice presented a serious challenge to the conformational change theory. Such conservation, Bruce argued, could only be explained if the infectious agent possessed its own informational molecule that was replicated and passed on from one infection and one host species to another.

Bruce's paper had a huge impact on many researchers. Chris Bostock, head of the division of molecular biology of the Institute of Animal Health (IAH), told an interviewer, "here you have PrP^{Sc} from several different species going into mice and you get the same biological properties. I think the people who support the protein-only hypothesis will find it difficult to explain that."[97] Even Charles Weissmann himself acknowledged, "her [Moira Bruce] results demanded a very satisfactory explanation. A very special effort would be needed in order to integrate them into the protein-only hypothesis."[98] Nonetheless, Prusiner summed up the meeting with an emphatic denial that scrapie and other diseases were caused by a viral agent. According to Sharon Kingman in her report for *Science*, he insisted, "all the data taken together argued persuasively that prions lack a nucleic acid".[99]

Nevertheless both sides proclaimed their triumph in this controversy. John Collinge, director of the prion research unit at St. Mary's Hospital Medical School in London and one of the foremost prion enthusiasts, argued that for many people, this was a key turning point in the prion versus virus argument.[100] On the other hand,

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[97] **Kingman, S.** (1993) *op. cit.* note 93 : 181
[98] *Ibid.*, 181
[99] *Ibid.*, 181
[100] *Ibid.*, 180

Moira Bruce remembers the meeting rather differently. She says, "it had dramatic effects on people like Charles Weissmann, Stan Prusiner. They just, for some reason, suddenly realised that this has to be explained somehow [...] In that meeting, everybody was talking about the strains, whereas, before this, everybody was just ignoring the whole issue [...] I brought it to the forefront, I think, as a very practical issue, and this approach can be very useful in a practical sense. So that is accepted, in that sense, we won! There is an acceptance that there is an informational component, and 'what it is' is another question."[101]

Despite both sides claiming victory in the great battle, nobody was actually a winner at the time. The controversy not only continued, but deepened; enmity between the researchers become, if anything, more intense. However, the general mood in the scientific community had been inclining gradually towards the protein-only theory, even though every experimental result could just as easily be read in favour of the prion-sceptics. As science writer Georgina Perry wrote in *New Scientist*, "Prusiner's heresy was to challenge the received wisdom [...] now, more than a decade later, this idea [protein-only theory] is slowly absorbed into mainstream thinking, helping researchers to understand fatal brain diseases."[102]

3. Winner takes all

3.1. Attempting to demonstrate that PrP is infectious

Following the 1993 Royal Society meeting, the efforts of the prion believers increasingly come to concentrate on attempts to demonstrate that the prion protein is itself infectious. As discussed above, one line of prion-sceptical research during the 1980s involved demonstrating that scrapie and CJD infectivity could occur in the absence of PrP.[103] Subsequently, after 1993, the prion sceptics continue to produce evidence suggesting that PrP might not be the infectious agent.

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[101] **Bruce, Moira E.** (1999) *op. cit.* note 15

[102] **Perry, G.** (1994) 'Mad brains and the prion heresy', *New Scientist* (28 May 1994): 32

[103] **Manuelidis, L., T. Sklaviadis, et al.** (1987) *op. cit.* note 51; **Sklaviadis, T.K., L. Manuelidis, E. E. Manuelidis** (1989) *op. cit.* note 55

In 1994, a neurologist at the Istituto Superiore di Sanita in Rome, Maurizio Pocchiari, claimed that he found very small, virus-like particles in brain samples from CJD patients.[104] This was quite similar to results produced in the same year by Heino Diringer at the Koch Institute at Berlin, who found similar particles in his hamster samples.[105] Furthermore, Pocchiari's team was also able to produce some more damaging evidence against the prion hypothesis. His team treated scrapie-infected hamsters with a drug, amphotericin B, which delays protein aggregation. He found that this delayed the build up of protease-resistant PrP and the onset of disease symptoms. However, it did not delay the build up of infectivity in the infected tissues. Pocchiari's team interpreted this as suggesting that, while the pathological form of PrP (PrP^{Sc}) is necessary for the development of disease pathology, it is not necessary for replication of the scrapie agent, i.e. this was another piece of evidence dissociating infectivity from PrP. They argued, therefore, that the proteinase-resistant portion of PrP^{Sc} is necessary for the development of the disease but that it is unlikely to be essential for scrapie replication.[106]

Prusiner recognised that this was a problem. This was particularly so as he had still not been able to demonstrate to his critics' satisfaction that pure PrP^{Sc} is itself infectious. Consequently, he realised that his theory would be stabilised on much firmer ground if he could demonstrate the transformation of PrP^{C} into PrP^{Sc} *in vitro*. Since the late 1980s, some researchers had focused upon attempts to convert the normal protein into an abnormal one in a cell-free system. This project had two aims. Firstly, it provided a basis for performing further chemical tests on the protein. More importantly, it offered a means of validating prion theory. If a brand-new PrP^{Sc} particle, created at the laboratory bench could be shown to be infectious, this would be strong evidence that protein in the absence of nucleic acid is the real agent causing the fatal diseases. According to Weissmann, "the experiment of the decade in this field will be to take biosynthetic PrP^{C} which you have made under conditions where

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[104] **Ozel, M., Y.G. Xi et al.** (1994) 'Small virus-like structure in brains from cases of sporadic and familial Creutfeldt-Jakob disease', *Lancet 344* (8927): 923-924

[105] **Ozel, M. and H. Diringer** (1994) 'Small virus-like structure in fractions from scrapie hamster brain', *Lancet 343* (8902): 894-895

[106] **Xi, Y.G., L. Ingrosso et al.** (1992) 'Amphorericin B treatment dissociates in vivo replication of the scrapie agent from PrP accumulation', *Nature 356* (6370): 598-601

there is no possible infectious nucleic acid around. And then wave your magic wand over the test tube, inject it, and find that it has become infectious. If that experiment is done, I think that 99.999% of the people in the field will agree. That's it."[107]

The trick would be to take biosynthetic PrP^{C}, which is known to be uncontaminated with nucleic acids, convert it into PrP^{Sc}, then demonstrate that this completely pure prion protein is infectious. The problem is, that this proved impossible to achieve. While it is possible to produce biosynthetic PrP^{C}, it proved impossible to convert it into infectious PrP^{Sc} by chemical means. Two of Prusiner's collaborators, Fred Cohen and Glenn Telling, attempted unsuccessfully to fulfil this aim. In an interview with Rosie Mestel in 1996, Cohen claimed that "we have managed to create material which is rich in β-structure, and we have created material which is protease resistant [that possesses some of the key physical and chemical properties of PrP^{Sc}]. But to date we have not created material that is infectious."[108]

Meanwhile, at the RML, a young biochemist, Byron Caughey, and an MIT chemist, Peter Lansbury Jr., were trying different way to convert PrP^{C} into PrP^{Sc} in test tube.[109] In 1994, at last, the collaborative team reported that they had succeeded in converting PrP^{C} to PrP^{Sc} in a purified cell-free solution. They prepared artificial PrP^{C}, radiolabeled it, and mixed it with PrP^{Sc} from infected hamsters. When they then digested the mixture with protease-K to remove the PrP^{C}, they found that some of the remaining PrP^{Sc} was radiolabeled, i.e. some of the PrP^{C} has been converted into PrP^{Sc}.[110] This was consistent with Prusiner's long-standing protein-only theory, because the conversion in a cell-free system implied that any possible small viral

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[107] **Mestel, Rosie** (1996) *op. cit.* note 72: 187; Almost all the interviewees whom I interviewed agreed with this argument. It seems to be a consensus amongst scientists that the crucial and conclusive experiment to prove the prion theory would be *in vitro* conversion.

[108] **Mestel, Rosie** (1996) *op. cit.* note72: 188

[109] This project began in the late 1980s. At that time, they attempted to construct the abnormal form of the protein from a cloned prion gene in a cell-free system. In 1988 they obtained the abnormal form of protein, but the newly constructed protein was not infectious at all. This led them to conclude that infectivity and PrP were two different things. [**Caughey, B., R. Race, et al.** (1988) 'In vitro expression of cloned PrP cDNA derived from scrapie-infected mouse brain: lack of transmission of scrapie infectivity', *CIBA Foundation Symposium* **135**: 197-208.]

[110] **Kocisko, D.A., J.H. Come, et al.** (1994) 'Cell-free formation of protease-resistant prion protein', *Nature 370*: 471-474; This experimental result was reported in the New York Times because it was assumed to be a crucial step to understanding how the normal protein was

components could be excluded, and the conversion explained solely by pure protein interactions. This was good news for Prusiner and bad news for the sceptics. However, problems now arose in demonstrating that the *new* PrP^{Sc} is infectious. The problem is that, in order to achieve transformation, a considerable quantity of hamster-derived PrP^{Sc} had to be added, and the proportion of new PrP^{Sc} was tiny in comparison. Consequently, any increase in infectivity, assuming that the new PrP^{Sc} was indeed infectious, was simply too small to measure. Here, David Bolton pointed out why the infectivity of the conversion experiment is not measurable:

> It's not that it has no infectivity, it's that you cannot measure its infectivity. It's a peculiar thing about the way the experiment is done. In Byron's experiment, you radio label some of the normal protein, so you have a relatively small amount of radio chemically labelled normal protein. And you add to that a very large amount of the abnormal form and you combine them in the test tube. And because the abnormal form is not radio chemically labelled, it is transparent when you do the separation and the autoradiography. So, if you combine them for a while and then test them for protease resistance, you will find that over some time, the radio chemically labelled normal protein goes from being completely protease sensitive to being some protease resistance. The problem is, when you go for infectivity, it is like weighing a man on a battleship. You have all the infectivity, the battleship that you have added, and now you have added one man to it. You cannot distinguish that.[111]

Byron Caughey also stated "until we or someone else can measure new infectivity the proof just isn't there."[112] If the researchers had been able to do so, and if the converted protein had been infectious, they would have had what they call "the ultimate proof of the protein-only hypothesis".[113]

In other words, this attempt to prove the infectiousness of PrP^{Sc}, like all other attempts, was a failure. Meanwhile, Prusiner's team was looking for a reason why the protease-resistant PrP that Cohen and Telling had produced might not be infectious. Cohen suspected that, while they had managed to produce a version of PrP with *some* of the properties of PrP^{Sc}, they had not achieved full conversion into PrP^{Sc}. Cohen told a reporter: "our suspicion is that there is some other molecule that

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transformed into the pathological form. [**Blakeslee, Sandra** (1994) 'New understanding of how a protein runs amok' *The New York Times* (16 August 1994)]

[111] **Bolton, David** (2000a) *op. cit.* note 39

[112] **Mestel, Rosie** (1996) *op. cit.* note72: 187

[113] **Rhodes, Richard** (1997) *op. cit.* note *20:* 207

is required for the really proper folding of PrP^C into a prion state." This was consistent with the results of another series of transgenic experiments that Prusiner's team had conducted around 1994. From early experiments done by Mike Scott, Prusiner's team realised that wild-type mice are normally resistant to infection with scrapie hamster-adapted scrapie agent (SHa). By contrast, if the hamster PrP gene was transferred into transgenic mice, referred to as Tg(SHaPrP) mice, the transgenic mice show hamster scrapie symptoms.[114] When an artificial host was constructed that contained hybrid genes for both mice and hamsters PrP, referred to as a chimeric gene, it was be susceptible to both mouse scrapie and hamster scrapie.[115] However, puzzling results occurred when Scott and another transgenic expert, Glenn Telling, extended this experimental system to the human genome. Around 1994, they were able to construct transgenic mice expressing human PrP^C [Tg(HuPrP)]. However, mysteriously, the transmission of human prion disease such as CJD failed in these transgenic mice. In contrast, in the case of transgenic mice expressing a chimeric mouse-human PrP gene, referred to as Tg(MHu2M), which means that transgenic mice contain a hybrid PrP gene of humans and mice, infection occurred quite effectively in these transgenic mice.[116] The researchers were left with the puzzle of explaining why solely human transgenes cannot show the infectivity of the disease, whereas if the transgene consisted of part-human and part-host genes, then infection occurs. Prusiner and Cohen thought that this phenomenon might be attributed to the involvement of unknown host encoded element – possibly an auxiliary non-PrP molecule, provisionally designated "protein-X", which participates in the formation of prions by interacting with newly translated PrP^C to facilitate its conversion to PrP^{Sc}.[117] According to Cohen, "the right answer was that even though proteins could

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[114] **Scott, M., D. Foster, et al.** (1989) 'Transgenic mice expressing hamster prion protein produce species-specific scrapie infectivity and amyloid plaques', *Cell 59* (1 December, 1989): 847-857

[115] **Scott, M., D. Groth, et al.** (1993) 'Propagation of prions with artificial properties in transgenic mice expressing chimeric PrP genes', *Cell 73* (4 June, 1993): 979-988

[116] **Telling, G. C., M. Scott, et al.** (1994) 'Transmission of Creutzfeldt-Jakob disease from humans to transgenic mice expressing chimeric human-mouse prion protein', *PNAS 91*(October 1994): 9936-9940.

[117] **Telling, G.C., M. Scott, et al.** (1995) 'Prion propagation in mice expressing human and chimeric PrP transgenes implicates the interaction of cellular PrP with another protein', *Cell 83*: 79-90

fold on their own, that in general they did not. In general, they used this assistant machinery. So the concept that we put forward was that it was unlikely that this process depended upon the prion protein alone entirely. And rather, that there were likely to be auxiliary factors that could play a role in this that would help one over the barriers. Or, prevent one from normally going over the barriers."[118] (See Figure 4)

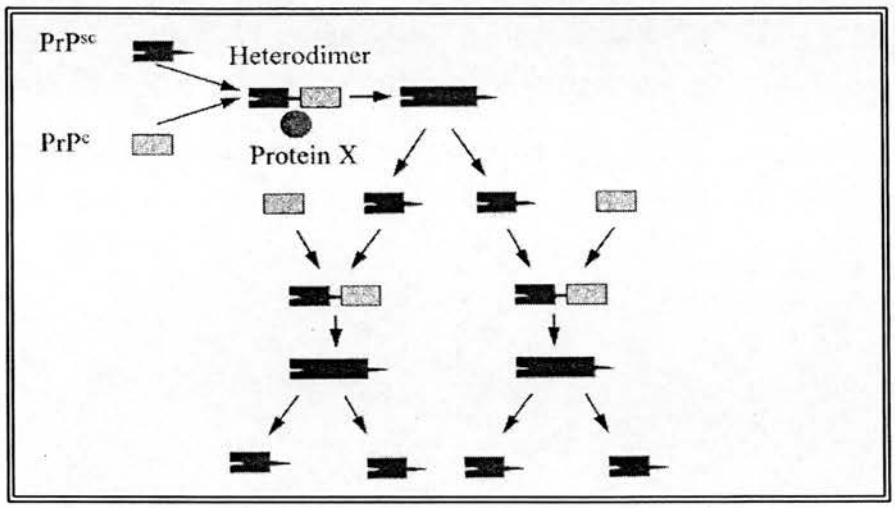

Figure 4: The basic illustration of prion hypothesis with protein-X. The molecules of PrP^{Sc} will combine with molecules of PrP^{C} to form heterodimers (mixed pairs). During the interaction, the PrP^{C} will convert to PrP^{Sc}. The two molecules of PrP^{Sc} are then able to separate and to go in search of further PrP^{C} molecules. Studies using transgenic mice suggest that another molecule, designed protein-X, may also be involved in the conversion process.[119]

Cohen consequently agreed that research perspective should be shifted from the molecular biological level to the level of protein folding mechanisms. This was quite a significant shift as far as Prusiner's perspective is concerned. For Prusiner, it was the first serious extension of his work from the molecular to the cellular level. Up until that time, Prusiner himself had not been interested in process such as protein interactions. However, when a protein-folding expert, Fred Cohen, became involved in prion research, the whole agenda of the research had to be extended. What Cohen and Prusiner were now interested in was the so-called protein kinetics. They assumed that proteins would not fold by themselves, and there had to be something else to promote protein foldings in the real cellular situation. When pathogens like

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[118] **Cohen, Fred** (2000) *op. cit.* note 88

[119] **Ridley, R. M. and H. F. Baker** (1998) *op. cit.* note 71: 138

prions are injected, or invade from outside, "you have a relatively short window of opportunity between which the agent has to establish productive infection. In the case of prions, it has to bind the PrP^C on a cell that is capable of replicating, it has to be internalised and start making more of it than is being degraded. If that is not happening in a short time, then the agent is eliminated from the body and the animal does not get sick."[120] Thus, in order to understand the process of the internalisation of exogenous malfolded prion protein and its interaction with the normal prion protein, it is necessary to involve various other factors at the cellular level.

However, this addition of a new layer of hypotheses in order to explain gaps in the prion theory failed to impress sceptics such as Manuelidis and Race. Race at the RML points out that the auxiliary factors that Prusiner now invokes are equally or perhaps more compatible with a viral aetiology. He claims that "I don't think there is really any good strong evidence for a 'protein-X'. Protein-X might actually be PrP. Yes, there's something else there. It could be some viral induced component, too."[121] Furthermore, Manuelidis thought that Cohen's hypotheses about helper molecules were simply intellectual acrobatics. She claims that she was unimpressed by the additional molecules and different classes of protease-resistant PrP molecules, some that are infectious and others that aren't. Manuelidis' criticism was that Prusiner's protein-X was getting into the realms of medieval thought processes. If you can't distinguish structurally between PrP gene and helper genes, then how do you know that they're really different?[122] She even argued that the X sounds a lot like a virus.[123]

As can be seen, whenever the prion group produced experimental results, and claimed that they had the momentum to prove their prion theory. Their results and speculations, however, were always flexible enough to be interpreted differently from the sceptical viewpoint. Nonetheless Prusiner and his prion theory (or protein only theory) became major reference points in the field. With the outbreak of BSE and nvCJD in the UK, his name and theory became circulated as a standard terminology in the public domain. In 1997 the whole credit for scrapie-like disease

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[120] **Bolton, David** (2000a) *op. cit.* note 39
[121] **Race, Richard** (2000) *op. cit.* note 19
[122] **Mestel, Rosie** (1996) *op. cit.* note72: 188
[123] **Manuelidis, Laura** (2000) 'The force of prions', *The Lancet 355* (10 June 2000): 2083

research went to Prusiner. On 6 October, the Nobel committee at Karolinska Institute, Sweden, announced that Stanley Prusiner had won the 1997 Nobel Prize for medicine for his work on prions.[124]

3.2. The triumph of the prion

Throughout all this work during the 1990s, the two camps of prion believers and prion sceptics failed to reach agreement on the meaning of their scientific results. For those most closely involved in work on scrapie and other supposed prion diseases, the evidence remained insufficient to decide conclusively one way or another. In 1994, for instance, the Chancellor of the University of California at San Francisco, Joseph Martin, who is also a neurologist, claimed that the prion hypothesis had stood the test of every experiment that could possibly be devised.[125] On the other hand, one of the sceptics, Robert Rowher, director of the molecular neurovirology unit at the Veterans' Affairs Medical Center in Baltimore, urged that the agent is a very hardy and robust virus.[126] Dissent still raged amongst scientists at the time.

From about that time onwards, however, influential agencies within the wider scientific community increasingly come to side with Prusiner and his once heretical suggestion that these diseases are caused by an infectious protein, in the absence of any nucleic-acid-based informational molecule. This growing acceptance of the prion hypothesis manifested itself in the form of numerous significant prizes given to Prusiner, among them a Gairdner Foundation International Award (1993),[127] the Richard Lounsbery Medal from the National Academy of Science (NAS),[128] a Charles

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[124] **Altman, Lawrence K.** (1997) 'US scientist wins Nobel Prize for controversial work', *The New York Times* (7 October, 1997)

[125] **Kolata, Gina** (1994) 'Viruses or prions: an old medical debate still rages', *The New York Times* (4 October, 1994): Science Section 1

[126] *Ibid.*

[127] The Gairdner Foundation is a non-profit corporation for research into biomedicine in the worldwide. See the Gairdner Foundation website. [www.gairdner.org]

[128] Richard Lounsbery Medal is awarded for stimulating research and encouraging reciprocal scientific exchanges between the United States and France. Prusiner was awarded this medal for 'distinct and exciting discoveries about the pathogenesis of neurodegenerative and malignant diseases. This award celebrates the power of modern molecular medicine in 1993' [**NAS** (2001) 'Richard Lounsbery Medal', National Academy of Sciences-Awards (www4.nationalacademies.org/nas/nasaward.nsf)

A. Dana Award for Pioneering Achievements in Health (1992),[129] and a Christopher Columbus Quincentennial Discovery Award in Biomedical Research from the National Institutes of Health.[130] Although his work was not conclusive and still controversial at the time, the Albert Lasker Clinical Medical Research Award Committee, which is believed by many to be the most significant biomedical science prize in the States,[131] and is generally viewed as a "predictor" of the Nobel Prize, announced that Stanley Prusiner was the winner of its prize in 1994. The committee also recognised that some scientists still considered Prusiner's work to be controversial. One of the committee members, Jordan Gutterman, professor of clinical immunology and biological therapy at the M.D. Anderson Cancer Center in Houston, stated that "obviously the Lasker jury did not feel that this is controversial. Even if the final proof is debatable, some of the most outstanding minds today think this is as solid as it can get."[132]

However, this winning of the Lasker award could not change the sceptics' mind. Robert Rowher, who is one of the diehard sceptics, referred to the prion theory as the cold fusion of infectious diseases. He also added that as such it demands scrutiny and scepticism until it is proven.[133] Indeed, even while Prusiner gained general credibility and awards from various foundations for his transgenic work, the sceptics continued to produce counter-experimental results against the prion theory. During

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[129] The Dana Foundation is a private philanthropic foundation with principle interests in health and education. The award has been running since 1986, and is for making innovative and pioneering achievements in health and education. Prusiner won this award for the discovery of a new disease pathogen, both genetic and infectious in nature, called the 'prion'. [**Dana.Org** (2001) 'The Dana Foundation', *The Dana Foundation* (www.dana.org)]

[130] **Spector, Barbara** (1994) 'Lasker Awards cite persistence of three scientists', *The Scientist 8* (17 Octorber 1994): 20

[131] The Lasker foundation was established in 1942 by Albert Lasker, the late owner of the Lord & Thomas advertising agency, and his wife Mary Lasker, who was an enthusiastic advocate of biomedical research.

[132] **Kolata, Gina** (1994) *op. cit.* note *125*

[133] *Ibid.* Gary Taubes wrote a famous prion sceptic paper in *Discover* (1996). This paper was so negative towards Prusiner that the latter rarely spoke to journalists from any publication thereafter. The main thrust of Taube's argument was that Prusiner's transgenic experiments did not conclusively prove his claim that the infectious agents were proteins *sans* nucleic acid, and that Prusiner only managed to publish his proof-of-prion paper, "After it had been rejected by the journal *Cell*. Prusiner managed to find a home for it in *the Proceedings of the National Academy of Science*, where it wouldn't have to be peer-reviewed." [**Taubes, Gary**

the 1990s, as we have seen, each camp of scientists continued to produce many experimental results, but in each case the evidence could be interpreted differently by their opponents. Both sides were struggling to convince the other, but in the context of the controversy, it was indeed hard to disprove and dismiss each others' interpretations. Despite the interpretative flexibility of these experiments, Prusiner and his prion alliance continued to gain credibility from the research community. As Laura Manuelidis complained when Prusiner won the Lasker award, the viral camp's prospects of further research funds to pursue the informational molecule were dwindling.

Nonetheless, Prusiner continued to gain support, and in 1997 was awarded the Nobel Prize. The Karolinska Institute announced, "Prusiner has added prions to the list of well known infectious agents including bacteria, viruses, fungi, and parasites. Stanley Prusiner's discovery provides important insights that may furnish the basis of understanding the biological mechanisms underlying other types of dementia-related illnesses - for example, Alzheimer's disease, and established a foundation for drug development and medical treatment strategies."[134] However, this announcement faced hostile criticisms. Many researchers thought that the infectious agent remained unknown, and there was some concern that the Nobel Assembly might be prematurely endorsing the controversial theory. Almost all the mass media reports stressed the controversial history of Prusiner's hypothesis, using words such as, "once-heretical theory",[135] "after years of heated debate",[136] "controversial research"[137] and so forth.

Accordingly, Laura Manuelidis at the Yale Medical School criticised the decision of the Nobel assembly, and claimed that she feared that the Nobel assembly's endorsement of the prion theory would stifle other avenues of further inquiries.

(1997) 'Nobel Gas', *Slate, Web-magazine* (10 October, 1997; slate.msn.com/HeyWait/97-10-10/HeyWait.asp)]

[134] **Karolinska Institutet** (1997) 'The Nobel Assembly at the Karolinska Institute has today decided to award the Nobel Prize in Physiology or medicine for 1997 to Stanley B. Prusiner', *Press Release* (6 October 1997)

[135] **Vogel, G.** (1997) 'Prusiner recognized for once-heretical prion theory', *Science* **278:** 214

[136] **Coles, H.** (1997) 'Nobel panel rewards prion theory after years of heated debate', *Nature* *389*: 529

Moreover, another prion sceptic, Ashley Haase, in the microbiology department at the University of Minnesota, said that he thought that the Nobel committee should have waited to make the award until there was proof that protein alone was capable of causing infection.[138] In spite of such strong criticisms, the Nobel committee and other general scientists expressed different views on this issue. Ralf Pettersson, the deputy chairman of the Nobel committee, even implied that persistent scepticism about prion had contributed to the spread of BSE to human beings. He claimed that the panel was not bothered by the unanswered questions. The committee was well aware of where the field stood. The details had to be solved in the future. But no one could object to the essential role of the prion protein.[139] He added, "during the whole of the nineteen-eighties, the prion was very controversial. Acceptance took a while. This could have delayed moves. It was more political decision about when to take action, and by then it was too late."[140] A Nobel laureate, David Baltimore, also supported Prusiner's winning, saying that all through the history of science there were people who kept their own faith for many years and lived through a period of opprobrium, and finally were discovered to be right.[141] When the Nobel assembly announced Prusiner's victory, Prusiner himself said, "concepts are vindicated by the constant actual data and independent verification of data. No prize, not even a Nobel Prize, can make something true that is not true."[142]

His triumph seemed to be decisive with the award of this Nobel Prize. However, it was not the end. Just as the Nobel Prize winner was announced in October 1997, another series of controversial experimental results came out. Prusiner's archrivals in NPU, Moira Bruce and her team, published further research on BSE and new variant CJD. Like her earlier work on BSE, this work once again raised the issue of strain variation in prion diseases and its conservation when those diseases were transmitted to new species – a phenomenon that, as we have seen, could not be

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[137] **Josefson, D.** (1997) 'The prion hypothesis is finally accepted by the establishment', *British Medical Journal* **315**: 972

[138] **Altman, Lawrence K.** (1997) 'US scientist wins Nobel Prize for controversial work', *The New York Times* (7 October, 1997)

[139] **Vogel, Gretchen** (1997) *op. cit.* note135: *214*

[140] **Rhodes, Richard** (1997) 'Pathological science', *The New Yorker* (1 December 1997): 54-55

[141] **Josefson, Deborah** (1997) *op. cit.* note *137*:972

explained by Prusiner's prion theory, and that seemed to demand the involvement of an informational molecule.[143] On this result, some commentators claimed "whatever the nature of the agent, our understanding of TSE biology is evidently incomplete".[144]

Nevertheless, the winner took all the credit for the discovery of prion disease. This was the case even though at the time, according to Richard Rhodes, only four of the fourteen major TSE research laboratories actually working on the infectious agent wholeheartedly espoused prion theory, nine others considered it unlikely, and one was undecided.[145] So why in the absence of conclusive evidence did scientific credibility swing to the prion theory? In the next chapter, we will attempt to find the answer for this question.

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[142] **Altman, Lawrence** (1997) *op. cit.* note 138

[143] **Bruce, M. E., R.G. Will et al** (1997) 'Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent', *Nature 389* (2 October, 1997): 498-501; At the same time, the link between BSE and nvCJD was confirmed by John Collinge's transgenic experiments. However, this experiment also raised another question about Prusiner's protein-X. Prusiner and his team suggested this additional concept to explain why transgenic mice possessing the human PrP gene were not susceptible to CJD. Collinge's team showed on the contrary that his transgenic mice with human prion gene without any additional chimeric gene did become infected by CJD. This experimental result was contradictory to Prusiner's one. [**Hill, A. F., M. Desbruslais, et al.** (1997) 'The same prion strain causes vCJD and BSE', *Nature 389*(6650): 448-50]. Although Collinge is one of the prion enthusiasts in Britain, his experimental result fuelled another controversy on protein-X.

[144] **Almond, Jeffrey & John Pattison** (1997) 'Protein only prions?', *Nature 389* (2 October 1997): 438

[145] **Rhodes, Richard** (1997) *op. cit.* note 140: 55

Chapter 9 – Molecularising prion disease

1. Introduction

As seen in the previous chapters, attempts to characterise the scrapie agent to everyone's satisfaction have so far been inconclusive, although the weight of opinion amongst scientists has come down on the side of Prusiner's prion theory. Many commentators have acknowledged that no crucial experimental result has yet been reached. When Prusiner suggested his idea in 1982, most scrapie researchers dismissed his idea as "heretical". However, within 20 years he has gained considerable scientific credibility from fellow scientists and the public alike. Correspondingly, his opponents, the prion sceptics, who were once the mainstream in this field, have been marginalised. Nevertheless, the sceptics continue to pursue their research project to prove their own theory. For the last twenty years, the opposing stances have not come to any point of agreement. Although each side can point to experimental results they consider crucial, the data are flexible and open to interpretation.

In this chapter, I am going to search for a plausible explanation of how and why the controversy was sustained over such a prolonged period, why opinion became so sharply polarised between prion sceptics and prion believers, and why the two sides held so fiercely to their respective opinions. Moreover, I will then explain why the prion advocates gained much wider credibility and support among influential sections of the scientific community than did the prion sceptics.

Through the prion controversy, the contending factions of scientists displayed divergent values, patterns of practice, rules of social relations, laboratory structures, and so on. This diversity of the two groups participating in the prion controversy can elucidate why they held so strongly to their divergent scientific beliefs about the scrapie agent.

Consequently, in the first sections of this chapter, we will explore the divergent styles of research programme, and the material and social circumstances that

influenced researchers to pursue these scientific programmes. Moreover, different patterns of persuasion will be discussed. In the later sections, we will examine why Prusiner's group won greater credibility among fellow scientists. In particular, I will argue that his methods and style of research owed much to the development and proliferation of a molecular biological approach that is closely associated with new patterns of organisational and social order in the sociological sciences. The proliferation of this molecular biological perspective is bound up with wider social transformation, which can be called the "molecularisation of biomedicine".[1]

2. Divergent styles of research programme

As seen in my earlier analysis of the closure of the Edinburgh-Compton debate in the 1970s, the Edinburgh group gained considerable credibility from the scientific community because, among other things, they had a broadly biological perspective that was in keeping with the approaches favoured by the British research councils.[2] The perspective of the Edinburgh group remained the predominant approach to scrapie and related diseases in the US as in Britain during the 1980s. In this context, however, Prusiner's early work began to diverge from other work on scrapie, in that it abandoned the broadly biological approach for a much narrower concentration on the biochemical aspects of the agent. Each party has since developed distinctive intellectual and methodological frameworks in the course of the dispute. Here I would suggest the controversy is actually sustained and promoted through the confrontation of these two oppositely patterned styles of research programme.

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[1] This notion is based on various historical analyses of the impact of the molecular approaches in twentieth-century biomedicine. Since the revelation of the structure and function of nucleic acids and proteins in the 1950s, the spectacular success of molecular biology has had a big impact on the whole field of biomedical science. This transformation has resulted not only from scientific success, but also from social and political change. Historians have used the term "molecularisation" in order to describe this radical transformation in science and society. [**Keller, Evelyn Fox** (1995) *Refiguring Life: metaphors of twentieth century biology* (New York: Columbia University Press); **Wright, Susan** (1994) *Molecular Politics: developing American and British regulatory policy for genetic engineering, 1972-1982* (Chicago: University of Chicago Press); **De Chadarevian, Soraya and Harmke Kamminga** (eds) (1998) *Molecularising Biology and Medicine: new practice and alliances, 1910s-1970s* (London: Harwood Academic Publisher)]

[2] For more detailed analysis, see chapter 5, 'How controversy ends: disputes on the nature of scrapie and their closure'.

As shown in the previous chapter, the two groups of scientists produced various experimental results, and each group believed that those results supported their own theories of the nature of scrapie. However, the experimental evidence failed either to decide unequivocally between the two sets of theories, or to establish common ground on which the two groups could reach consensus. This was because the two groups evaluated the data with reference to quite different criteria, which in turn were embedded in two different research programmes which might be characterised as ***generalist biological*** and ***specialist biochemist*** programme. The sceptics' programme of scrapie research has concentrated on the issue of the complicated phenomena of ***disease;*** in other words, the main issue was about how the disease replicates in the host, and how the agent and the host genes interact. On the other hand, the prion group has mainly focused on the issue of the biochemical structure of the ***agent.*** The different primary goals and research orientations led the two groups to construct quite distinct experimental programmes. The prion sceptics' concentration on the nature of the disease led them to explore a variety of biological phenomena including nature of the agent; whereas Prusiner's concentration on the nature of the agent, led him only secondarily to ask about how it is implicated in the phenomena of disease. The two factions thus pursued strikingly distinct ranges of intellectual and methodological issues.

These distinct patterns of theoretical and experimental practice can best be characterised in terms of distinct styles of research.[3] Recently, there is a significant work done by Jonathan Harwood. In his work, he addresses how differently patterned cultures emerged and were maintained. His work embraces historicity of styles and co-existence of different styles of thought. Unlike previous studies of style, he stresses the importance of not reifying styles, as if they were things that possessed the power to shape scientists' thought and action.[4] Instead, we ought to see style as

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[3] **Harwood, Jonathan** (1987) 'National styles in science: genetics in Germany and the United States between the World Wars' *Isis 78*: 390-414; **Harwood, Jonathan** (1993) *Styles of Scientific Thought* (Chicago: The University of Chicago Press)

[4] There are several studies of styles, which are attempts to apply the concept to various socio-cultural phenomena. For instance, Karl Mannheim adopted the concept from art studies to identify a variety of social groups' articulated thought (see **Mannheim, Karl** (1953) 'Conservative thought' Essays in Sociology and Social Psychology (London: Routledge and

indicators that thought is patterned.[5] According to Harwood, 'styles of scientific thought exist when particular ontological and/or epistemological assumptions recur in a variety of scientific domains and those assumptions differ from one group to next'. He attempts to exemplify his theory by focusing on the development of genetics in American and Germany in the early twentieth century. He analyses the development of genetic research, and comparing it with the social, educational and institutional background of different research community. He remarks that national differences of scientific traditions were manifestly maintained in their practice. Furthermore, it is demonstrated that different cognitive patterns associated with scientists' social background can be identified within a particular national context.[6]

In this chapter, I extend Harwood's work on styles of thought to the domain of scientific practice. The domain where scientific theory is constructed and every actor's interests are maintained and crated is the field of practice. This kind of work is also found in Joan Fujimura and Danny Chou's work.[7] They claimed that the case of debate on the origin of AIDS could be elucidated in terms of different patterns of practice, in which they conceptualised styles of scientific practice. Fujimura and Chou claimed that "style of practice are historically located and collectively produced work processes, methods, and rules for verifying theory. [...] Style of practice implies that practices of theory construction, adjudication, and maintenance

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Kegan Paul): 74-164). Also, Ludwik Fleck drew different styles between scientific thought and religious or metaphysical thought-collective. However, his sociological analysis is quite idealistic: the thought collective was sometimes claimed to dictates and coerces the overall behavioural patterns of scientific practice (**Fleck, Ludwik** (1979 [1935]) Genesis and Development of a Scientific Fact (Chicago: The University of Chicago Press)). For more general studies of styles in social studies of science, **Sontag, Susan** (1968) 'On style', Sontag, Susan (ed.) *Against Interpretation* (London: Eyre & Spottiswoode); **Bloor, David** (1978) 'Polyhedra and the abominations of Leviticus', *British Journal for the History of Science 11*: 245-272; **Harwood, Jonathan** (1986) 'Ludwik Fleck and the sociology of knowledge', *Social Studies of Science 16*: 173-187; **Lowy, Illana** (1988) 'Ludwik Fleck's role in society: a case study using Joseph Ben-David's paradigm for a sociology of knowledge', *Social Studies of Science 18* (4): 625-651; **Barnes, Barry** (1994) 'Cultural change: the thought styles of Mannheim and Kuhn', *Common Knowledge 3* (2): 65-78.

[5] **Harwood, Jonathan** (1993) *op. cit.* note 3: 15

[6] **Harwood, Jonathan** (1987) *op. cit.* note 3

[7] **Fujimura, Joan H. and Danny Y. Chou** (1994) 'Dissent in science: styles of scientific practice and the controversy over the cause of AIDS', *Social Science and Medicine 38* (8): 1017-1036; **Fujimura, Joan H. and Danny Y. Chou** (1995) 'Styles of practice in HIV/AIDS research', *Techniques and Culture 25-26*: 195-244

are situated actions".[8] The styles are embodied in practice, in particular, specific scientific programme. As you will see, different styles of scientific programme in the prion controversy pervaded their distinct ways of conducting experiments, interpreting data, using techniques, constructing models, and organisational structure.

2.1. Generalist biological programme of the prion sceptics

As we have seen, the prion sceptics have mainly focused on disease aetiology, pathogenesis and agent-host interactions as well as the nature of the infectious agent. For instance, since Dickinson's group began their research project in 1957, they have been broadly concerned with the "nature of the disease process".[9] Indeed this biological and pathological orientation was made clear in the articles that opened the prion controversy in 1982.[10] More specifically, for Dickinson and his colleagues, the biological diversity of the agent provided the main point of attachment for elucidating the nature of the infectious agent. Since the 1960s, they had recognised that there are many strains of scrapie. They also realised that this phenomenon of strain variation posed a major challenge for the prion theory. For this reason, Dickinson and his colleagues stressed the importance of understanding the nature of agent variation. As Dickinson remarks in the BSE Inquiry, this distinguished his own approach from that adopted by Prusiner:

> The NPU [Neuropathogenesis Unit, Dickinson's laboratory] had distinguished itself from most work worldwide, when most people were saying: "we want to know what the nature of this agent is". And I, starting as a geneticist, said: "I think a more fundamental question is: "what is the nature of agent variation?" [...] It is very important distinction. If you think about it, there are those who claim, I think prematurely, that they know what the nature of the agent is in chemical terms. The outstanding question is very much: " what are strain differences?" "What is the nature of agent variation?"[11]

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[8] *Ibid.*, 1020-1021

[9] **Dickinson, Alan G.** (1999b) Interview with author (Dunbar: 15 September 1999)

[10] **Dickinson, Alan G.** (1982) 'Scrapie: strategies, stalemates, and successes', *Lancet* (29 May 1982): 1221-1223; **Kimberlin, R. H.** (1982a) 'Scrapie agent: prions or virinos?', *Nature* 297 (13 May, 1982): 107-108; **Kimberlin, R. H.** (1982b) 'Reflections on the nature of scrapie agent', *Trends in Biochemical Sciences* 7: 392-394

[11] **Dickinson, A, G.** (1999) 'Transcription of oral hearings: day 31', *The BSE Inquiry* (11th June 1998: http://www.bseinquiry.gov.uk/evidence/trans/transcripts.htm): 4-5

In this respect, they developed a distinctive intellectual and experimental programme. Interestingly, the Edinburgh researchers refer to their overall experimental project as a "generalist project". As George Outram remarks, "scientists themselves fall into two kinds of fundamental types generally, generalist and specialist...our culture, I can say, is generalist. You've got a scientist who knows a lot and is very good at some techniques and extremely complicated equipment. Then you have generalist".[12] In this statement, Outram not only identifies himself as a generalist, but identifies a generalist orientation as fundamental to the entire research programme that he and his Edinburgh colleagues proved. Outram explains the whole philosophical ground of their research project. He remarks as follows:

> The danger with this approach [biochemistry, immunology, virology and molecular biology apply here] is that in order to get meaningful answers the right questions must first be asked and, if scrapie is an unprecedented phenomenon, then the inbuilt assumptions of any developed methodology will effectively prevent the agent from 'answering' the questions we address to it. In short, we require something more ***general***, i.e., less specialised, which will survey the whole phenomenon and so enable us to identify or devise such specialised techniques as will be really appropriate.[13]

On philosophical grounds, the Edinburgh researchers thus concluded that before exploring the specific characteristics of the agent, their research should aim at providing a general understanding of the disease. Thus, "this should provide a broad biological base against which the disease could declare itself in its own terms rather than those imposed by some other inappropriate system."[14] For the Edinburgh researchers, strain variation was the best subject to examine, because an understanding of strain variation would throw light on the whole biological mechanism of the disease.

Moreover, this distinctive intellectual orientation of the sceptics was also embodied in their research methodology. As we have seen, Dickinson and his

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[12] **Outram, G.W.** (1999) Interview with author (5th August, 1999: Edinburgh)

[13] **Outram, G.W.** (1980) 'Mouse scrapie: black-box models and the slow encephalopathies', F. C. Rose and P.O. Behan (eds) *Animal Models of Neurological Disease* (Bath: Pitman Medical Limited): 360

[14] *Ibid.*, 360

colleagues have been to observe as many aspects of strain variation as possible, including incubation time, lesion profiles and the affects of host genotype. For this purpose, they needed an animal model that would make it possible both to display the widest range of strains possible, and to standardise the biological circumstances in which those strains were investigated. For these reasons they chose to work with mice, spending nearly ten years breeding, selecting and inoculating a variety of in-bred strains that reliably and reproducibly manifested the various phenomena that interested them.[15] In this respect, it is notable that through succeeded in transmitting scrapie into hamsters, and in demonstrating that the disease incubated more quickly than in mice, he chose not to adopt the hamster as his preferred experimental animal. The reason was simple: while at least twenty different strains of scrapie could be studied in mice, only two of these could be transferred into hamsters. Thus, despite the greater speed with which hamster experiments could be performed, they simply did not display the range of phenomena that the Edinburgh researchers considered it imperative to observe.[16]

2.2. Specialist biochemist programme of the prion group

Compared with the prion sceptics' general biological perspective, Prusiner's work concentrated primarily on studying the agent, while aetiological and pathological concerns were secondary. On the whole, Prusiner was interested less in how the agent manifests itself in the ***form of disease***, than in simply asking what the ***agent is***, particularly in chemical and molecular biological terms. In his early research, Prusiner focused on revealing the biochemical structure of the agent. His priorities were made clear when he responded to the criticisms of the prion sceptics in 1982. Prusiner claimed:

> Knowledge of the structure of the agent is mandatory before attempting to design studies that can answer such fundamental and critical questions as: (1) how does the

[15] For more detailed description and discussion of the procedure for constructing their animal experimental model, see chapter 3, 'Genetic research into scrapie at the Moredun Institute, Edinburgh, 1964-1979'.

[16] **Kimberlin, R. H., C. A. Walker** (1977) 'Characteristics of a short incubation model of scrapie in the golden hamster', *Journal of General Virology* 34: 295-304

> agent replicate, (2) in what cells does it replicate, and (3) how does it produce neurological dysfunction?"[17]

Prusiner's view of the objective of his research was thus the precise opposite of what Outram suggested. While Outram suggested, as we saw above, that the primary object of research should be a general understanding of ***the disease***, Prusiner claimed that the priority of research should be understanding of the ***structure of the agent***.

Conversely, by concentrating on such a specific research aim, Prusiner and his team were able to bring a range of specialist methods to bear on their research. As one of Prusiner's colleagues, Mike Scott, remarks:

> We're all becoming specialist in some way. I think you have to go with technology, and the technology is molecular biology, rational drug-design, genomics, NMR, X-ray crystallography, recombinant antibodies etc...I think anybody who doesn't embrace the new "specialist" biotechnology is doing himself or herself a disservice.[18]

For Prusiner and his team, understanding the molecular structure of the agent by using various techniques of biochemistry was the first step toward exploring the whole biological mechanism of the disease. Since he launched his research project to isolate the agent from the cellular components in the early 1970s, Prusiner has consistently adopted some of the most innovative biochemical and molecular biological techniques in a sustained assault on this single problem.

In this context, Prusiner's preferred choice of experimental animal also distinguished him from the sceptics. As we have seen, the Edinburgh group favoured mice because they revealed a wide range of scrapie phenomena. Prusiner, by contrast, was initially interested in laboratory animals only as a means of performing bioassays of the scrapie agent after exposure to various physical and chemical treatments. For this purpose, the hamster with its shorter incubation time, was far preferable to mice. Then, since 1989, Prusiner's team has constructed transgenic animal models as a means of focussing yet more closely on the

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[17] **Prusiner, Stanley B.** (1982) 'Research on scrapie', *Lancet* (28 August 1982): 494

[18] **Scott, Mike** (2000) Interview with author (18 August, 2000: University of California, San Francisco)

proteinaceous character of the scrapie agent. At each stage of his experimental project, he has adapted animals more as a means of pursuing particular biochemical techniques than for the biological phenomena they reveal. In this sense, Prusiner's experimental system is more specialist-oriented than that of the Edinburgh group.[19]

2.3. Virino/Prion: naming as declaration of scientific programmes

As we have seen, the prion group and sceptics had quite distinctive experimental programmes. Under those different scientific programmes, each party decided to adopt a distinctive name for the agent. Dickinson's group called it a virino, and Prusiner called it a prion. This can be seen in both cases as a sort of declaration that they were doing some important and new.

When Dickinson dubbed the agent a "virino" in 1979, he intended to draw attention to the importance of the objects they were studying – a distinctive family of viruses with peculiar characteristics and possibly wider medical significance.[20] Dickinson and his colleague, George Outram, stated that "an appropriate name for this class of agent would be 'virinos', which (by analogy with neutrinos) are small, immunologically neutral particles with high penetration properties but needing special criteria to detect their presence".[21] In this sense, Dickinson intended to stress the remarkable properties of the agent – hence the reference to the neutrino, one of the most elusive, basic, uncharged particles of matter.[22]

Interestingly, the term virino acquired a further layer of meaning following Prusiner's adoption of the term "prion" in 1982. Dickinson had from the beginning supposed that the scrapie agent must contain nucleic acids, but in 1979 this

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[19] It should be noted that the demarcation between generalist and specialist programmes should not be perceived as an absolute distinction. At some level of organisation and collaboration, any such divergence is at most a matter of degree, not one of kind. For instance, Dickinson admitted that the Edinburgh team's progress was to an extent delayed by the lack of biochemists, i.e. they recognise and rely on specialist skills. However, in this context, my demarcation of generalist and specialist programmes indicates distinct tendencies of research objectives, methodologies, and experimental systems that are best captured by the term "style".

[20] **Dickinson, A. G., G.W. Outram** (1979) 'The scrapie replication-site hypothesis and its implications for pathogenesis', S. B. Prusiner & W. J. Hadlow (eds), *Slow Transmissible Diseases of the Nervous System* **2:** 13-31 (London: Academic Press)

[21] *Ibid.*, 30

[22] **Cooke, Jennifer** (1998) ***Cannibals, Cows, and the CJD Catastrophe*** (London: Minerva): 103

supposition was shared by most of those working on scrapie-like diseases. The term "virino" was therefore adopted primarily to emphasise how the scrapie agent differed from conventional viruses. When Prusiner decleared his own willingness to suppose that the agent might not contain nucleic acid, however, Dickinson reasserted the term "virino" precisely because it signified similarity to conventional viruses in the crucial aspect of possessing a nucleic acid genome.[23]

From its inception, the name "prion" – to simplify a proteinaceous infectious particle - was controversial. At this point, the naming of the agent became an important issue in the scientific community. Some now claimed that before a clear picture of the nature of the agent was drawn, it was premature to name the agent.[24] However, Prusiner baptised the agent in his *Science* article. Prusiner wanted to mark a significant break with the established biological orientation to scrapie-like diseases. He chose the term prion to reflect this. In his article, he suggested two possible models of prion: the first was that of a small piece of nucleic acid, which is "buried within a tightly packed protein shell". The second model was of an infectious agent devoid of nucleic acid.[25] Prusiner himself recognised that this second hypothesis was heretical, marking a significant break with conventional knowledge. As the editor of *Chemical and Engineering News* stated in 1982, prion is a challenge to an even greater biological wisdom. The editor claimed, "a life form that does not contain nucleic acid, Prusiner admits, is clearly heretical. It is a central tenet of biology that nucleic acids – DNA and RNA – are the universal bearers of the genetic code and, hence, are necessary for life".[26] Prusiner was careful at this stage not to declare a preference for one or the other of these two hypotheses. But by deliberately emphasising the proteinaceous character of the agent he flagged up his empiricist refusal to prejudge

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[23] **Dickinson, Alan G.** (1982) *op. cit.* note 4

[24] According to Richard Rhodes, Gajdusek claimed in an interview to have told Prusiner that he preferred to give disease agents a proper name only when he was sure what their molecular structure was. Gajdusek says, "I made this point repeatedly with him [Prusiner], explaining that it was premature to name them since, although we knew they had no nucleic acid, we were not sure of their biochemical nature." **[Rhodes, Richard** (1997) *Deadly Feasts: tracking the secrets of a terrifying new plague* (New York: Simon & Schuster): 161-163]

[25] **Prusiner, S. B.** (1982) 'Novel proteinaceous infectious particles cause scrapie', *Science* **216** (4542): 141

[26] **Anonymous Editorial** (1982) 'Possible new life form tinier than virus', *Chemical and Engineering News 60*: 4

the nature and constitution of the agent. Thus, Prusiner admitted that "current knowledge does not allow exclusion of a small nucleic acid within the interior of the particle".[27] Prusiner's close collaborator, Stephen DeArmond, confirms Prusiner's caution in this respect. He remarks, "Prusiner will not commit himself until the data is there. And actually, in 1982, they didn't even know where the protein was formed. It could have formed in a virus".[28] Nonetheless, Prusiner's willingness even to suggest that the scrapie agent might not contain nucleic acid was a bold more, which his deliberate decision to privilege the proteinaceous character of the agent made clear his commitment to biochemical methods rather than biological dogma.[29]

In effect, the term "prion" and "virino" thus came to stand, not just for opposing ideas about the nature of the scrapie agent, but for two distinctive approaches to investigating and elucidating that nature. For Prusiner, the biochemical evidence of it, proteinaceous character was paramount. Theoretical presuppositions must be suspended which further biochemical investigations were pursued. Dickinson, by contrast, was concerned to take into account not just all that was known biologically about the agent – its peculiar immunological characteristics, its pathological behaviour – but also what was known about other viral diseases that scrapie in some ways resembled in some ways differed from.

3. Material circumstances

In the previous section, I characterised the two factions in the prion controversy in terms of the distinct intellectual and methodological programmes that they pursue and styles they favour. I argued that the prion group pursued what we might call a specialist programme, which the prion sceptics adopted what can be defined as a generalist biological programme. I will now go on to explore some of the circumstantial factors, which have been influential in informing and sustaining the

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[27] **Prusiner, S. B.** (1982) *op. cit.* note 25: 141

[28] **DeArmond, Stephen** (2000) Interview with author (18 August 2000: UCSF, San Francisco)

[29] Hence, the title of his article in *Science:* "***Novel*** proteinaceous infectious particles cause scrapie".

divergent programmes in the prion controversy. In this section, I will look at the role of funding structure.

In the case of the prion sceptics, it is notable that they are generally working in secure posts in long-term government-funded institutions, committed among other things to managing and understanding disease as a broadly biological and ultimately economic phenomenon. On the other hand, Prusiner and his colleagues are largely dependent upon short-term grant funding, which tends to encourage the pursuit of more narrowly defined and self-contained research projects. These differences are clearly apparent in the different kinds of questions the two factions ask and in the methods they use - including the very long-term genetic experiments favoured by the prion sceptics, and Prusiner's concern to produce rapid results.

3.1. Long-term government funded research of the prion sceptics

Most prion sceptics belong to government-funded institutions such as NPU (funded by the Biotechnology and Biological Science Research Council), IBR (Institute for Basic Research, funded by New York State Government), and RML (Rocky Mountain Laboratory funded by National Institutes of Health, namely, NIH). Under this funding structure, researchers have a stabilising post in general. For instance, at NPU (previously the Moredun-ABRO collaborative unit), most members at the institute have a permanent post. For two decades, it scarcely ever happened that anybody left or did other outside work; Dickinson, Fraser, Outram, Bruce, and Kimberlin, all continued to work together until their retirement. In her interview, Moira Bruce says, "everybody has a permanent job. There is no problem about the short term contracts. It was stabilised funding. There was always the possibility that the Research Council might withdraw funding, but there wasn't grant-funding system within the BBSRC institutes at that stage. It was fairly open-ended. It was remarkably relaxed".[30]

Within this funding structure, it was possible to conduct long-term experiments in the genetics and pathology of scrapie. Indeed such experimental projects were conditional on stable and uninterrupted funds to guarantee continuity of work. In

[30] **Bruce, Moira** (1999) Interview with author (9 June 1999: NPU, Edinburgh)

particular, genetic experiments into mouse scrapie took a considerable time to yield experimental outcomes, because of the nature of the material and the need to control a wide range of variables. As we have seen, Dickinson's group took at least ten years to perfect their genetic experimental system. This kind of experiment would have been nearly impossible to accomplish under a short-term grant system.

Another interesting consequence of government funding is that it has tended to encourage the pursuit of a broad understanding of disease, including its biological aspects. Government funding is generally informed by economic concerns. For instance, the Moredun-ABRO research unit was set up specifically for the purpose of solving the problems of economic loss in the agricultural industry due to epidemics of scrapie. As seen in chapter 5, there were quite large scale scrapie epidemics in Britain and America in the late 1950s and early 1970s, which led both governments to launch research projects to solve this problem.[31] In order to address such practical problems, researchers sought to understand the disease itself, not just the mystery of the infectious agent. This explains why most sceptics have focused on the problem of understanding the ***disease***, not just the agent.

3.2. Short-term grant funded research of the prion group

On the other hand, in the case of Prusiner's group, we find a very different picture from that of the NPU. Their research funds have mostly depended on short-term grants from the NIH and private funds. This is a general tendency in the American research system, particularly in university-based research institutes. Moreover, the American system attaches importance primarily to the accomplishments of individual grant holders not institutes. This individualisation is a consequence of post-war federal support for scientific research in the States. As Susan Wright points out, during the post-war era in the 1950s and 1960s, distribution of research money was centred on agencies such as the National Institutes of Health (NIH).[32] The empowered NIH allocated research money not to universities or department heads, but to individual researchers, in the form of grants for specific projects. Under this funding system, one of the most important factors for research is

[31] For more detailed discussion, see chapter 5, 'how controversy ends'.

individual outstandingness. Researchers must demonstrate the significance of their project in the short term. Otherwise, there is no possibility of getting large amounts of research funds. Research projects, in general, consequently, tend to be quite narrowly defined and self-contained.

Prusiner's laboratory at UCSF is university-based. This means that he has had to raise his own research funds from NIH and other sources. It is therefore not surprising that he has tended to concentrate specifically on elucidating the nature of the scrapie ***agent***, and on developing quick and efficient methods for doing so, including his hamster model and his incubation time bioassay method. Indeed, Prusiner has proved himself to be highly effective not just in raising research funds, but in managing them. His skill in the management of his laboratory is deemed to be unique,[33] including the organisation of intricate networks of collaboration, and the planning and supervision of every stage of the resulting experiments. In this matter of managerial style, too, he differed from the prion sceptics, as we shall see.

4. Social circumstances

I will now explore how different styles of scientific programme are associated with different forms of social relations within the two factions. The two parties differed in terms of the patterns of interaction and collective practice in each laboratory. Robert Kohler's work on the moral economy of laboratory culture in the case of the *Drosophila* group provides a remarkably good model for investigating such different patterns of scientific practice.[34] As Kohler states, unique moral conventions regulate access to the tools of experiments, in the sense that members have to commit themselves to the unstated rules of the laboratory. In a similar fashion will now explore the social and moral order that obtained in the laboratories of the two factions in the controversy, and will show how they related both to the

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[32] **Wright, Susan** (1994) *op. cit.* note 1: 28-29

[33] **Bolton, David** (2000a) Interview with author (IBR, New York: 31 July, 2000)

[34] **Kohler, Robert E.** (1994) *Lords of the Fly: Drosophila genetics and the experimental life* (Chicago: University of Chicago Press).

different research programmes explored by the two groups and to the social and economic circumstances in which they worked.

4.1. The communitarian relation of the prion sceptics

The prion sceptics, working within long-standing research teams, tend to pursue not just a collaborative but in effect a communal mode of research. Not only do they pursue research programmes that bring together individuals with a variety of skills for the purpose of illuminating the whole disease process, but they also all tend to share in negotiating, agreeing and overseeing that research programme. For instance, in Dickinson's group in Edinburgh, everyone in the group enjoyed free and unhindered access to the instruments of knowledge production. For that to work, it was necessary for all the members to have a general understanding and knowledge of the whole experimental project. This is because genetic experiments usually need a long-term commitment, so the process of experiments has to be rigorously controlled. A fault occurring in the middle of the experiment could ruin at least a year's work on the project. Therefore, all the members have to understand the general procedure of the whole experiment.

Importantly, there is a sense that this is a shared project, and indeed that all will succeed or fail together. This is bound up with the nature of the long-term experiments they undertake, which involve considerable investments of time and energy from several members of the team. For this reason, openness is a positive virtue, which helps to avoid collective disaster. Hence, in his interview, Dickinson insists that "people were told the day they were employed, once we'd chosen them, 'you will make mistakes, everybody makes mistakes, and what we want you to do when you find a mistake, is come and show us. We know it will happen and we will work it out together. You must not correct mistakes on your own.' "[35] Thus, when there is a problem in the process of experiment, the members sort it out together. For this co-operative work, each researcher must have at least a general knowledge of the whole procedure and basic principle of the experimental design. There is another good example of this kind of social relations between researchers in NPU. The

[35] **Dickinson, Alan G.** (1999b) *op. cit.* note 9

building design of the NPU is open and transparent. It is deliberately designed that way to avoid workers being isolated. In his interview, Dickinson also notes "if you go to NPU, you will find that the lab areas, the walls are all made of glass. It is a single unit and people can be in social contact with one another and they are doing jobs which have been thought out from the point of view to be as efficient, as quiet, as compatible as possible."[36]

That this ethos of openness and communitarian social relation is not restricted to the NPU, but holds good throughout the whole prion-sceptic community, and even beyond. It is seen, for instance, in the willingness of the various groups to provide research materials including scrapie strains and mice to one another. This relates to another element of the moral and social order, namely the distribution ownership of knowledge. Dickinson's group needs a functionally coordinated division of labour because of the complex nature of genetic research. Because of the cooperative nature of the work, the ownership of the research goes to the community itself. Finding new products such as strains of laboratory mice and the scrapie agent is not thought to be an individual achievement. Individual ownership is discouraged in NPU. Even when collaborating, the Edinburgh researchers dispatched their strains of the agent to other laboratories without charge. Merz in IBR remarks that "there was sample material that came back and forth between Edinburgh and the United States, primarily from Edinburgh to us, because they had strains, they had type strains of the agent."[37] Here is a passage from the *BSE Inquiry* showing the basic attitude on sharing knowledge products:

> Dr. Bruce: We produced in-house antibodies, and in fact the first antibody that was available was an extremely good antibody which is being used to this day.
> Professor Ferguson-Smith: Where was that made?
> Dr. Bruce: At NPU
> Professor Ferguson-Smith: Made by you?
> Dr. Bruce: By Christine Farquhar
> Mr. Walker: So it is used by you, is it used by others as well? Have you supplied it to others?

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[36] *Ibid.*

[37] **Merz, Patricia** (2000) Interview with author (27 July 2000: IBR, New York)

Dr. Bruce: Yes, it has been distributed very widely throughout the world.[38]

Even at the peak of the prion controversy in the mid-1980s, Dickinson's group sent all the strains of the agent to other research groups in the world including their opponents, Prusiner's group, though Prusiner did not conduct any strain work with those resources.[39] One of the prominent researchers in NPU, Hugh Fraser, claims that "Dickinson sent Stan Prusiner all the strains of scrapie that we had, except agent 87A, because 87A was difficult to handle. In 1987, I took them over and sent them to different laboratories throughout all the world, and one person who received more than anybody else was Stan Prusiner."[40] In conclusion, the prion-sceptic community shares a specific form of social relations, which I would like to call a ***communitarian social order***.

4.2. Contractual social order of the prion group

By contrast, Prusiner's reliance on short-term grants inclines him to pursue very different kinds of relations with his colleagues and collaborators. The social order in Prusiner's group inclines towards a more autocratic way of working. The laboratory structure is based on the expertise system. Prusiner's early collaboration with the RML is illuminating in this respect, in that he did not become absorbed into their programme, but rather used the RML simply as a place to carry out bioassays, i.e. as in effect a measuring instrument for the biochemical experiments he conducted in UCSF. Short-term contract funding has also reinforced this system of short-term collaboration, in that Prusiner not only tends to design his experiments around clearly specified technical questions and specific technical procedures, but also tends to bring in already-trained specialist collaborators (post-docs or established researchers) on contractual terms to provide the skills that he lacks. In this context, moreover, research instruments are used for highly specific purposes. Consequently, not every member of the team is allowed open access to all of the equipment. Each

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[38] **Fraser, Hugh, Jean Manson, et al** (1999) 'Transcription of oral hearings: day 23', *The BSE Inquiry* (11th June 1998: http://www.bse.org.uk/evidence/trans/transcripts.htm): 21

[39] **Dickinson, A. G. and G. W. Outram** (1988) 'Genetics aspects of unconventional virus infections: the basis of the virino hypothesis', Greg Bock and Joan Marsh (eds) *Novel Infectious Agents and the Central Nervous System 13* (Chichester: John Wiley & Sons): 88

expert only deals with their own esoteric instruments, so sometimes one worker in the group may not understand how to operate another's experimental instruments. This fact could be useful in understanding the culture of contractual expertise that operated in Prusiner's laboratory. While any sudden drop in the number of members from Dickinson's NPU is rarely observed, because of the nature of the co-operative procedure of the experimental system, in Prusiner's group there are numerous cases of discharge from the laboratory such as Michael Bolton, Paul Bendheim, Frank Masiarz, Karen Hsiao, Michael McKinley, and so on. This is because most researchers were post-doctoral fellows on two-year contracts, so after expiry of their contract period, researchers had to find other professional posts. However, Michael McKinley's case gives us an interesting clue for understanding their social order; he was a second-in-command in the lab for ten years, and co-editor of a volume about prions with Prusiner.[41] Prusiner's close collaborator, Stephen DeArmond, stated that McKinley was loyal to Prusiner's ideas, and made an immense contribution to development of prion theory. However, in 1991, all of sudden, McKinley dropped out of this field. McKinley was an expert in electron microscope research. But, around 1990, Prusiner's overall project shifted from basic biochemical research to biotechnological projects including transgenic experiments. This being so, McKinley's specialty suddenly became less significant, whereas the role of newcomers such as Mike Scott and Karen Hsiao, who were specialists in advanced biotechnology became influential. According to DeArmond:

> I had long talks with Stan about that, because I didn't understand it at first. Because McKinley was very loyal, had done a lot of things. Stan's argument about that was that McKinley had not progressed. He was still stuck at a very basic level of doing electron microscopy and some very basic preparations, but wasn't contributing new ideas, and was costing us a small fortune [...] At least that is what Stan tells me.[42]

Another notable feature of Prusiner's style of research is the quite marked division of labour and expertise among the collaborating scientists. The laboratory in San

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[40] **Fraser, Hugh** (1999) Interview with author (30 June 1999: NPU, Edinburgh)

[41] **Prusiner, S.B., M. McKinley** (1987) *Prions: Novel infectious pathogens causing scrapie and Creutzfeldt-Jacob disease* (New York: Academic Press)

[42] **DeArmond, Stephen** (2000) *op. cit.* note 28

Francisco consisted of several sub-groups, all highly specialised in their own subjects, and each with their own specific ways of solving research problems, depending on their specialties. Again, DeArmond states on this issue:

> Let me tell you that the four of us are really the centre of all of the projects. Stan [Prusiner], Fred [Cohen], Mike [Scott] and me, attend nearly all of the meetings, and I have been with the projects the longest, and we really discuss everything that is going on. Each one of us has our own direction that we are an expert in. It is like a soccer team or anything, each one of us are specialised. The whole team is working together to get goals, but each one of us approaches it in a different way, but to get the goal we have to work together, we are always passing the ball around to each other to set up for the goal. So, it is essentially that way, it is a true team effort.[43]

The highly specialised divisions in San Francisco are a prominent feature. By contrast, which the sceptics have their own specialised subdivisions such as pathology, electron-microscopy, virology and so forth, these divisions are still flexible enough for members sometimes to move from one division to another.

We also need to understand how the division of labour in Prusiner's laboratory is coordinated in order to produce coherent research. Prusiner is himself remarkably inventive in devising experiments and exploiting new methods. And his control of funds gives him considerable power to ensure that other scientists carry these experiments through for him.

Social relations within Prusiner's laboratory, and between Prusiner and his collaborators, are thus not communal or mutualistic, but rather are contractual. They are about an exchange of money for skills, conducted between atomistic individuals each pursuing their individual interests. This reinforces the tendency towards a specialist division of labour. It also reinforces competitions between even collaborators. There are several sources of evidence for the individualistic disposition. First, while the British scientists share their basic resources with other groups in the world, Prusiner's group regards even current collaborators as potential competitors. This can be summed up in a word, ***co-opetition,*** that is basically a combination of "cooperation" and "competition", and that, according to one of

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[43] *Ibid.*

Prusiner's collaborators in UCSF, Fred Cohen, is used in the Bay area.[44] This implies that the practitioners always keep in their mind that their collaborators can be possible competitors in the field. Consequently, even though they have a collaboration, they maintain a high degree of secrecy and privacy. This attitude is observed in the case of the collaboration with Leroy Hood's group in California Institute of Technology (Caltech). When Prusiner was collaborating with Hood's team in Caltech for sequencing the protein chains in the early 1980s, one of his postdoctoral researchers, Michael Bolton, wanted to move to Hood's laboratory for the sequencing project. However, Prusiner did not want him to move, because Prusiner thought that there could be possible competition between the Prusiner and Hood teams in the future. Bolton says in interview:

> Within Stan's laboratory, I always felt that information was shared very readily. At least in the first few years. In the last year, I began to feel there was some secrecy ongoing. And that is maybe one of the reasons that I left. One of the things that I was most interested in was working on the sequencing of PrP. I went with Stan down to Caltech to meet with Leroy Hood, to work on the collaboration. When we came back, I said this would be a good thing for me to do, I'd like to go down there and work on that. He was not enthusiastic about my idea, and it turned out he sent his technician, Darlene [Groth] to do this. And that didn't please me because I felt that was something I really wanted to work on. He said no, you shouldn't do that, Leroy Hood has a very competitive lab or something, you wouldn't do well down there – I don't know what it was. But anyway, he discouraged that.[45]

Even within Prusiner's laboratory the flow of information was controlled by the senior level. As mentioned before, Prusiner's team in San Francisco consisted of four different subgroups which worked together in long-term collaboration: Prusiner's team in the Institute for Neurodegenerative Disease (IND); DeArmond's team in the neuropathology department; Cohen's group in the department of cellular and molecular pharmacology; and Scott's team in the neurology department.[46] Most

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[44] **Cohen, Fred** (2000) Interview with author (22 August 2000: UCSF, San Francisco)

[45] **Bolton, David** (2000a) Interview with author (31 July 2000: IBR, New York)

[46] Currently the collaboration at UCSF has been expanded, so more senior members are involved in the whole research project. For instance, computational structural studies (Dr. Fred E. Cohen), neuropathology (Dr. Stephen J. DeArmond), x-ray crystallography (Dr. Robert Fletterick; Biochemistry & Biophysics Department), NMR spectroscopy (Dr. Thomas James), cell-free synthesis (Dr. Vishwanath Lingappa; Physiology Department). [See the main

important issues and the agenda of the project were discussed in meetings of the senior scientists, and on some occasions, information was kept confidential. According to Bolton, when Prusiner launched his collaborative work with Charles Weissmann for finding the prion gene, the result of the collaboration was kept secret for a while. Bolton states, "that collaboration started a year or so earlier when Bruno Oesch came from Zurich to the lab [...] When they went back, and this is part of the information that was being kept very secret, so even though this was a collaboration between Weissmann's lab and Stan's lab, there were some of us in the lab that didn't know what was going on. We sort of knew, but we weren't privy to the results."[47]

Moreover, the relationship of collaboration could be very fragile. Around the early 1990s, the Prusiner-Weissmann collaborative team produced impressive results showing that the PrP gene knockout mice do not have susceptibility to scrapie. After that there were some uncomfortable arguments between Prusiner and Weissmann, because Weissmann claimed the patent of the knockout mice. Here, DeArmond describes the situation:

> Charles [Weissmann] was getting over $100,000 a year to do work in collaboration. Which was why it was such a problem when Charles Weissmann wanted to patent the knockout mouse. That was a project that was beginning here. And Stan said he needed to have one of his fellows have a project. So, Stan said, OK, go ahead and do it. And as soon as he does that, he wants to patent the knockout mouse without even acknowledging Stan, and then he started publishing papers on his own.[48]

The issue of patenting has become increasingly significant in science, particularily in relation to the growth of the biotechnology industry. As Dorothy Nelkin and Lori Andrews point out, biomedical science is the field of the "genetic gold rush". The researchers associated with biotech companies are receiving enormous benefits. According to Nelkin and Andrews, the *Genetic Engineering News*

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homepage of the Institute for Neurodegenerative Disease (IND); www.som.ucsf.edu/orus/ind]

[47] **Bolton, David** (2000a) *op. cit.* note 45

[48] **DeArmond, Stephen** (2000) *op. cit.* note 28. The patent of the PrP knockout mice is owned by Charles Weissmann and his colleagues in Zurich. [US patent number: 5698763: 'Transgenic animals lacking prion proteins', US Patent and Trademark Office (http://www.uspto.gov)]

now publishes a list each year of "molecular millionaires".[49] The patentship is a good indication of the degree of individual ownership. A count of the number of patents the scrapie researchers have registered, the distinctive patterns that characterise the prion group and the sceptics.

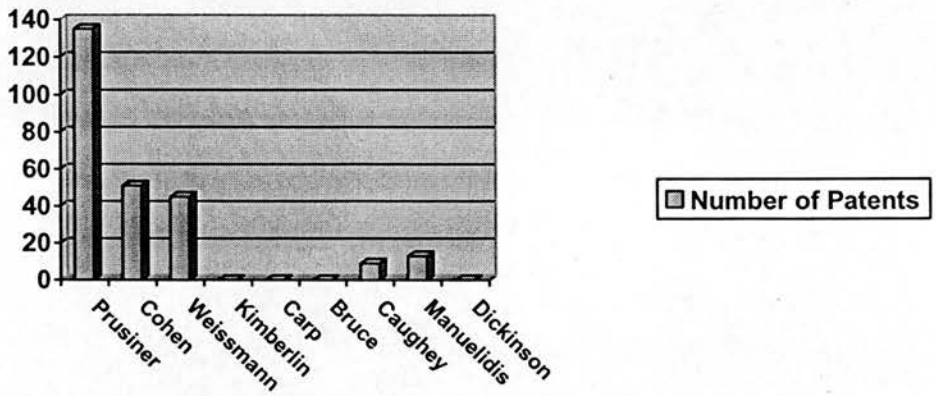

Table 1. Number of patents[50]

As can be seen in Table 1, according to the patent database of the UK Patent Office, Prusiner owns the highest number of patents, 135 in all, while prominent sceptics such as Dickinson, Bruce, Kimberlin, and Carp do not hold any patents. Furthermore, Prusiner's collaborators hold more patents (e.g. Cohen (51) and Weissmann (45)) than do other sceptics (e.g. Manuelidis (13) and Caughey (9)). From these records, it is evident that the prion sceptics are not productive in the commercial sense, whereas the prion group is active in commercialising their experimental achievements. I would suggest that the sceptics' lack of patents may reflect their patterns of ownership more generally. As discussed above, the sceptics, particularly those at NPU, discouraged individual ownership of the knowledge products. This might have resulted in the lack of patents. Conversely, it is precisely individual ownership that promotes the taking out of patents, as it apparent in Prusiner's laboratory. The tension between Prusiner and Weissmann resulted from this context. Of course, differences in numbers of patents might reflect different

[49] **Andrews, Lori, Dorothy Nelkin** (2001) *Body Bazaar: the market for human tissue in the biotechnology age* (New York: Crown Publishers): 46

institutional policies (which I have not investigated), but they seem also to reflect the informal culture of two different communities.

These examples show the underlying moral order in Prusiner's laboratory with regard to ownership. What leads the two groups of researchers to take such different attitudes towards the ownership of intellectual properties? On the one hand, the Edinburgh scientists tend to have a sense of communal ownership of the products of their experiments. On the other hand, Prusiner's group competes with other groups of scientists, even when they are collaborators. In the wider context, such different attitudes can be accounted for by two factors. Firstly, as mentioned briefly, the different culture of the funding system probably led them to have different attitudes. The American funding system encourages individual competition for research money. Once you succeed in getting grants from NIH, then your research achievements can be directly commercialised by patenting. By contrast, long-term government funding of institutes tends not to encourage such individual enterprise. Rather, funds go to the department or institute. As a result, a communal spirit is more likely to be fostered in such institutions. This difference cannot be generalised, but in this context, the two groups show totally different attitudes to the ownership of their knowledge products. Secondly, as will be discussed later, the commercialisation of biomedicine also encourages an individualistic way of research. Leon Rosenberg, the dean of the Yale University School of Medicine, says, "biotechnology has moved us, literally or figuratively, from the classroom to the boardroom and from the *New England Journal* to *Wall Street Journal*." [51] The commercialisation of life sciences promotes the individual researcher as can be seen in the case of the prion group.

The specific social relations to be found in Prusiner's laboratory thus encourage a high degree of secrecy and privacy, the pursuit of private gain through patents, and individual willingness to end the relationship when their partners are no longer useful to them. What ties the whole thing together is Prusiner's central role as dispenser of funds, employer and director of researchers. In this context, I would

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[50] The data are surveyed from the patent database of the UK Patent Office [www.patent.gov.uk] and the European Patent Office [www.european-patent-office.org]

[51] **Andrews, Lori, Dorothy Nelkin** (2001) *op. cit.* note 49: 46

suggest that Prusiner's laboratory can be characterised in terms of a *contractural form of social relations.*

The material and social relations that exist in the two laboratories are thus bound up with the kind of knowledge or other scientific products the two groups produce. Thus, the publicly-funded mutualist communitarian prion sceptics are interested primarily in producing knowledge of a group of diseases of purportedly social and economic significance. Prusiner and his collaborators on the other hand are interested in producing not just knowledge, but also techniques and material products that can be owned and exchanged or sold for personal gain – including cutting-edge technical skills, but also patentable processes, mice, genes and so forth.

5. Different directions for persuasion

Since the prion controversy began around 1982, the contenders have attempted to occupy the dominant position by persuading fellow researchers in the immediate research community and the wider public. Both parties have developed distinctive strategies of persuasion which, notably, are oriented in opposite directions. In the case of the prion group, their direction of persuasion is mainly oriented towards those outside their immediate research community – in particular, those we might call "disciplinary neighbours".[52] Sometimes this specific tendency is attributed to personal disposition; for example, many people commented that the leader of the group, Stan Prusiner, is very outgoing. It is not merely a matter of personality, however. Rather it is an outcome of the strategy the group has used. On the other hand, Dickinson and his allies tend to concentrate on persuading those inside the scrapie research community.

This difference in persuasive orientation is closely related to the social and economic conditions of the two groups. As we have seen, the prion sceptics are a stable group with relatively long-term stable government funds. In this situation, they can establish their own long-term projects, and rarely need to look outside for support, for assistance or indeed for approval or criticism of their work. On the other

hand, the prion group relies on short-term grants from government agencies and private funding sources. This situation forces them to continuously take on new people, enter into new collaborations, and endeavour to raise funds for the next round of research. Whereas the prion sceptics are largely self-sufficient, Prusiner has to wheel and deals make and fulfill contractual promises, self-promote and so on. In this context, persuasion is an important part of simply keeping his research enterprise going. Whereas the prion sceptics negotiate a common set of aims and values among themselves, Prusiner is continuously having to convince funding bodies to fund him and potential collaborators to join him. In this sense, Prusiner has to sell his project, not least to other scientists.

In the following section, I will explore these distinct patterns of persuasive practice in more detail.

5.1. Prion sceptics: orientation towards the immediate community

It is notable that most prominent prion-sceptcal scrapie researchers are quite rigorously critical of each other. Even within particular research groups, criticisms and struggles are common. One of the prominent scrapie researchers in the pre-prion era, Gordon Hunter, explains why this is so:

> It is partly the nature of the beast: if you set up a large experiment and then have to wait six or eight months or even longer for disease to appear, it is not conducive to a calm life if halfway through this period you realise on reflection that there has been a fault in the experimental design. This is combined with the excitement generated by the realisation that you are working right on the frontiers of knowledge in a field important to medicine, agriculture, and basic science. You have all the ingredients for the development of any extreme quirks of temperament.[53]

The leader of the NPU group, Alan Dickinson, is a typical example. According to Hunter, Dickinson has been described as the conscience of scrapie research, and certainly he was conscientious in his sustained criticisms of others' work. [54] Sometimes his criticisms of other researchers could be particularly harsh: for

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[52] I use this term to refer to scientists in neighbouring fields, who do not belong to the immediate community of researchers in scrapie-like diseases.

[53] **Hunter, Gordon G.** (1993) *Scrapie and Mad Cow Disease: the smallest and most lethal living thing* (New York: Vantage Press): 108

instance, in 1964, the meeting organisers from the Agricultural Research Service (ARS) at Washington were astonished to witness the violent arguments between the British scrapie workers, including dramatic walk outs and scathing criticism of each other's work.[55]

Dickinson's orientation of persuasion has always been toward the insiders of the community. Members of the group of prion sceptics rarely publish review papers on the scrapie related diseases for the purpose of introducing the diseases to a wider public (see Table 2). Rather, opinions are mainly exchanged within the immediate research community. This may be an effective means of understanding the esoteric features of the diseases, but it is not so useful for promoting their ideas to a wider public. Dickinson notes that in the beginning, when scrapie research was just being set up, the size of the immediate community was very small, but brought together scientists from various backgrounds with various criteria for approaching the disease.[56] Consequently, an initial aim was to negotiate agreed methods and standards of research. Criticism within the community should be rigorous in order to consolidate and refine the collective research project. The intensity of this internal debate meant they tended to neglect possibilities for persuading those outside the community. Moreover, with their stable long-term public funds, they do not need to look outside for support. Meanwhile, the introspective and self-referential debates within the scrapie community resulted in the development of esoteric terminology, which outsiders found hard to understand. Even Dickinson's loyal colleague, Moira Bruce, acknowledges that Dickinson's terminology was a bit obscure. She says, "a lot of people didn't understand what Dickinson was talking about."[57]

There is another reason why prion-sceptical scrapie researchers are oriented towards their own immediate community. Many scrapie researchers who belong to the sceptics' camp have grown up with the subject. Again, this reflects to social and economic conditions: the sceptics have stable funding system, and newcomers are

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[54] *Ibid.*, 98

[55] The meeting was held under the heading of *scrapie seminar* that was sponsored by Agricultural Research Service (ARS), US Department of Agriculture at Washington between 23rd and 30th January 1964.

[56] **Dickinson, A, G.** (1999) *op. cit.* note 11: 8

[57] **Bruce, Moira** (1999) *op. cit.* note 30

recruited into long-term employment. The majority of researchers have a PhD degree specifically on the subject of scrapie, and most are educated in the institution in which they subsequently work. Hugh Fraser, Moira Bruce, Richard Kimberlin, and Robert Somerville, all did PhDs on scrapie-related research at the Moredun Institute or IRAD at Compton. This is in sharp contrast to Prusiner's group, who never had PhD students in their institute, although their laboratory is based on the University of California. Consequently, from the beginning of their career, the prion sceptics have been acculturated into sharing the same standards, methods, and interests as their immediate colleagues.

The pattern of rigorous exchange between insiders is also found in the pattern of collaborations. One notable characteristic of the prion sceptics is that collaborations were conducted exclusively between the immediate research groups. The leading sceptic group at Edinburgh, NPU, had a long history of collaboration with Richard Carp's group at the Institute of Basic Research (IBR) in New York. The IBR group has already established and started research on scrapie in the early 1970s. One of the researchers in IBR, Pat Merz, says, "oh, we always had good collaborations [...] Alan [Dickinson] used to visit about once a year. Richard Kimberlin would be here about once a year. There would be a lot of discussion about things that were going on; helpful ways in directions, scientific directions and interpretations."[58] During the 1980s, the predominant collaborative pattern was for scrapie research groups to work with each other; collaboration with outside groups was quite a rare event. There were collaborations between NPU and RML (Rocky Mountain Laboratory) at Montana, IBR and the Yale group led by Laura Manuelidis during the 1980s. Those collaborations were basically not between scrapie researchers and their disciplinary neighbours, but between the insiders.

From those examples, we can conclude that the prion sceptics have tended to be rigorous and exclusive when exchanging and circulating their opinions. They are relatively detached from their disciplinary neighbours and the general public. Their rigorous way of reviewing each other's work seemed to play a positive role in

[58] **Merz, Patricia** (2000) *op. cit.* note 37

consolidating the newly emerging research network in the early days. However, this tendency has also resulted in isolation from the general public.

5.2. Prion group: orientation towards the disciplinary neighbours

By sharp contrast, Prusiner and his colleagues exhibit quite different patterns of persuasion from the sceptics. Where the sceptics tend to be inward looking, Prusiner's orientation is outward looking. A number of factors can help to explain this. In part, it may be attributed to his failure to win acceptance from the scrapie research group – not least because most immediate researchers in the community thought that his new concept, prion, was premature and deviated from conventional knowledge. As we have seen in the chapter on the prion controversy, Prusiner was severely criticised by his immediate colleagues. Prusiner himself remarks on the situation in the early 1980s: "[when] I introduced the term 'prion', [it] set off a firestorm. Virologists were generally incredulous and some investigators working on scrapie and CJD were irate."[59]

More importantly, his outward-looking tendency is closely bound up with the social and economic conditions under which he tends to work. As mentioned, his research has mainly been based on short-term grants. Consequently, he has had constantly seek funding for new projects. This in turn has meant canvassing support from other scientists, not least from potential collaborators whose specialist skills might be valuable in developing further research projects. In this respect, Prusiner has had to work hard to convince funding bodies and other researchers. In particular, the nature of his scientific programme has forced him to look for support from his disciplinary neighbours. He has sought to persuade not just the insiders but also the disciplinary neighbours.

In this situation, Prusiner is quick to recognise that he needs the support of the wider scientific community. One of the most effective ways in which he has secured such support has been by encouraging wide usage of his term, "prion" by publishing papers and presenting at conferences. During the early days of the prion controversy, Prusiner attended many conferences to give talks about his prion hypothesis, and

vehemently attempted to spread his idea. Some researchers found his talks to be like near-religious experiences. Ashley Haase, a former collaborator, says, "they're a repetition of the notion that the prion is the infectious agent. What happens to people who have to listen to this stuff is that they come away with the impression that the slow virus problem has been solved."[60] In his publications and presentations, he creates an "aura of inevitability" around his use of the term "prion". Although his idea is still controversial in the scientific community, he represents it as if it is already proved.[61] In her interview, Moira Bruce summed up Prusiner's way of presenting his case as follows:

> I think they [Prusiner's group] did a lot of hard work. It was very good work. But mostly I think it was salesmanship, he is a salesman [...] Have you seen Prusiner's presentation? I think his talks may be quite impressive to people who know nothing about him and his work. They are all confusing and his presentation is quite extraordinary. He has a lot of cartoon characters on his slides. It is silly...never mind.[62]

This way of presenting his ideas became a major subject of criticism by the sceptics. One of Prusiner's adversaries, Merz, says, "it is very simple, you can watch him at a meeting, major meeting. He is an MD, PhD, and he is a neurologist. He is very outgoing. He makes sure he meets all the editors of all the journals. He makes sure that he is in touch with whoever is going to be there that is a top-notch person. [...] 'oh, I've got to tell you about what I did and what I have found, what I am doing! See how great this is!' That's basically how it happens."[63]

Another notable aspect of Prusiner's self-promotion among his disciplinary neighbours is his use of public relations (PR). From the beginning Prusiner decided that he should run his scientific programmes like a business concern. Particularly within a short-term contractual funding environment, he realises that self-promotion

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[59] **Prusiner, Stanley** (1997) 'Stanley B. Prusiner-autobiography', *Nobel e-museum* (The Nobel Foundation: http://www.nobel.se/medicine/laureates/1997/prusiner-autobio.html)

[60] **Taubes, Gary** (1986) 'The game of the name is fame. But is it science?', *Discover* (December 1986):46

[61] Prusiner's rhetorical strategy of creating an "aura of inevitability" is discussed in Carol Reeves' analysis. Although she focuses merely on the rhetorical feature of the prion, it gives valuable insights. For more details, see **Reeves, Carol** (2002) 'An orthodox heresy: scientific rhetoric and the science of prions', *Science Communication 24* (1): 98-122

[62] **Bruce, Moira** (1999) *op. cit.* note 30

is vital. As DeArmond mentioned, "what he is a genius at, and probably even better at, is organising. If he were in a US company, he would be the President, and he would be making more money than anybody else. He would be Bill Gates."[64] Early in his programme, Prusiner hired a PR consultant under the name of laboratory manager in order to help convince private foundations and the public. Although nowadays big biotechnology companies and big laboratories routinely have public relations consultants, at the time it was unusual. Prusiner's unprecendented innovation provoked suspicion and criticism from many scientists. However, his sympathisers took the view that if scrapie research costs millions of dollars to move the project forward, this was the only practical way to raise funds. According to Bolton, "[the claim that Prusiner hired a PR consultant] is true, but I wouldn't say that was a bad thing. If you want to look at it that way, Stan [Prusiner] was probably 10 or 15 years ahead of his time, because I would bet a lot of big laboratories now hire fund-raising consultants. [...] You couldn't research just by writing a NIH grant, or asking some foundation for 50 or 100,000 dollars. So he just devoted his whole focus to raising money."[65]

As well as adopting a business style of management in his scientific programme, Prusiner also promote his ideas by using the popular mass media. For instance, in 1982, two months before his prion article was published in *Science*, he announced his idea in the *San Francisco Chronicle*. The headline was "Tiny life form found."[66] Prusiner remarked in an interview with Gary Taubes that "they put my picture and prions in the upper left hand corner of the front page on Friday. Reagan was on the right...that kind of thing did more than anything I could ever do. The prion became a household word among biologists immediately. They didn't even have to read *Science*."[67]

Between 1982 and 1985, his idea was reported by several newspapers from the *New York Times* (7 times), and *Scientific American* (3 times) to the *Reader's Digest* ("Killer disease from the dawn of time"). While such publicity-seeking roused other

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[63] **Merz, Patricia** (2000) *op. cit.* note 37
[64] **DeArmond, Stephen** (2000) *op. cit.* note 28
[65] **Bolton, David** (2000a) *op. cit.* note 27
[66] **Perlman, David** (1982) 'Tiny life form found', *San Francisco Chronicle* (19 February 1982)

researchers' antipathy, the prion nonetheless quickly became an accepted word for referring to the scrapie-like diseases.

Meanwhile, Prusiner has also energetically promoted his ideas within more specifically academic media. Interestingly, Prusiner has published many more review articles than his critics have. This strategy has done much to spread his ideas and concepts to the disciplinary neighbours. Between 1982 and 1989, according to the *Biomed* database, Prusiner published 16 review papers, whereas Kimberlin (2), Dickinson (0), Marsh (0), Carp (2), and Gajdusek (7) published far fewer review papers. You can see the tendency in the Table 2:

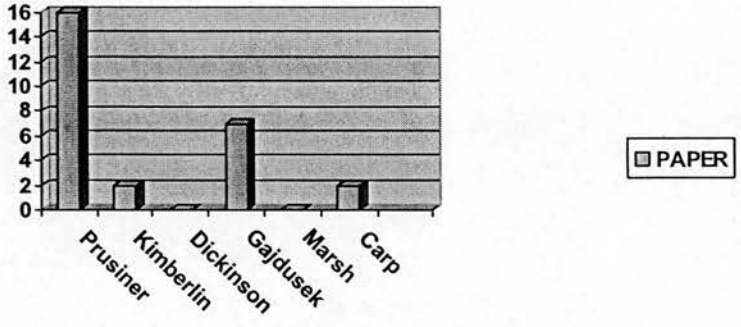

Table 2: Number of Review paper/total paper between 1982 and 1989[68]

Furthermore, Prusiner's group displayed an extroverted tendency in their pattern of collaboration. As have seen, the prion sceptics show an endogamous pattern of collaboration. Their communication network is exclusively centred upon their immediate research community. However, Prusiner's group had collaborations with disciplinary neighbours such as biochemists (Leroy Hood), molecular biologists (Charles Weissmann), Molecular geneticists (George Carlson), protein chemists (Fred Cohen), and pathologists (Stephen DeArmond). The collaborators are specialists in subjects that have no intrinsic relationship with the scrapie-like diseases. Indeed, before Prusiner asked them to collaborate, most of them had little or no knowledge about the scrapie-like diseases, or at most very basic knowledge on the subject.

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[67] **Taubes, Gary** (1986) *op. cit.* note *60*: 33

[68] The survey is based on the *Biomed* database between 1982 and 1989. [www.biomed.niss.ac.uk]. This specific period is selected, because all the main figures were

Nonetheless, Prusiner manages to collaborate with those scientists successfully. One benefit from this collaborative pattern is that Prusiner can recruit new researchers from outside of the community. As mentioned, Prusiner's laboratory does not have any PhD students. Instead, he tends to bring in already-trained specialist collaborators (post-docs or established researchers) on contractual terms to provide the skills that he lacks. All of the researchers in Prusiner's group are recruited from different disciplines and academic background. Again, this is closely associated with the situations in which he is located. Short-term contract funding has underlined Prusiner's tendency to buy in specific techniques and methods on a short-term basis.

From those different directions for persuasion between the prion group and prion sceptics, it is interesting to note that the overall map of consensus demonstrates its different directions for persuasion. As mentioned in the previous chapter, the prion hypothesis becomes a powerful mainstream view in the scientific community. This was materialised when Prusiner won the Nobel Prize in 1997. Although we can say that a great deal of the disciplinary neighbours accepted Prusiner's theory, the core-set of TSEs researchers remained divided.[69] The majority of the core-set of research community rejected Prusiner's idea. Division of opinion within the core-set of TSE researchers is still an issue. For instance, at a recent symposium, another Noble laureate Kurt Wüthrich pointed out that Prusiner's key concept, infectious prion protein is simply a build-up of garbage.[70] Despite the fact that Wüthrich contributed to the modelling of a three-dimensional structure of prion protein, he is still critical of the prion theory, arguing that we must understand the function of the

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actively involved in the controversy during this period. For instance, Dickinson retired from the directorship of NPU in 1989.

[69] The concept of core-set is first argued by Harry Collins. In his work on gravity waves, he defines core-set as follows: firstly the core-set of scientists are those who are actively involved in experimentation or observation. Secondly, they are making contributions to the theory of the phenomenon or of the experiment. I think the definitions of the core-set provide a good concept for this divisive phenomenon in the prion controversy. For more detailed, see **Collins, H.M.** (1981) 'The place of the core-set in modern science: social contingency with methodological propriety in science', *History of Science* 14: 6-19

[70] **Aguzzi, A. and M. Heikenwalder** (2003) 'Cannibals and garbage piles', *Nature* 423 (8 May 2003): 127-129

normal prion protein before we can understand prion diseases.[71] Interstingly, the wider acceptance of the prion theory is mainly related to the disciplinary neighbours. In contrast, the core-set is divided and majority of them rejects his theory.

6. Prusiner joins the molecular biological bandwagon

As we have seen, Prusiner lost the support of the scrapie research community in the early stage of the prion controversy. Though besieged by sceptics, however, he escaped the siege by collaborating with scientists outside the scrapie community. Since then, he has tended to address himself to scientists amongst the disciplinary neighbours as well as the members of the immediate community. He has been remarkably successful in attracting potential collaborators who are located outside the scrapie research community, and he has succeeded in making his work well known and in convincing many that it is valuable. This has been invaluable in winning him the widespread support that he and his ideas now enjoy in the scientific community as a whole.

In remains to ask just why the disciplinary neighbours should in turn have inclined to the prion theory? I will argue this relates closely to kinds of scientific products that Prusiner's laboratory produces. More generally, I will suggest that Prusiner's style of practice is in keeping with the way that many areas of biomedical science are moving. Molecular biological approaches, in particular, are very closely linked to commercialisation of modern biomedicine. Many of the people who pursue this approach are becoming increasingly influential within science – not least because they are becoming increasingly rich and increasingly closely connected to other powerful institutions in industry and government. Prusiner has had dealings with many of those people – hiring or collaborating with them, buying or selling scientific

[71] Wüthrich won the Nobel Prize for his development of nuclear magnetic resonance spectroscopy for determining the three-dimensional structure of biological macromolecules in solution. Furthermore, around 1996, he applied his NMR technique to reveal the three-dimensional structure of the prion protein. For a more detailed description of his contribution to prion research, see **Segal, Jérôme and Eric Francoeur** (forthcoming) 'Visualizing prions: graphic representations and the biography of prions', Eve Seguin and Carol Reeves (eds)

products, and so on. Indeed, his own ways of working epitomise the values of this market-oriented new scientific culture, while his ability to claim if not to prove fundamental breakthroughs in understanding important diseases serves to vindicate the whole enterprise.

During the 1980s and 1990s, the so-called molecularisation of biology was accelerated by the application of various new techniques. Joan Fujimura has described how with the commitment of one research group after another to the pursuit of proto-oncogenes in cancer research, molecular biological research became a bandwagon.[72] "Large numbers of people, laboratories, organisations, and resources became committed to one approach to a problem."[73] A crucial element in this convergence of scientific interests was the availability and adoption of standardised technologies such as NMR (Nuclear Magnetic Resonance), PCR (Polymerase Chain Reaction), transgenic technique, and so forth. Indeed, as Steve Sturdy argues, standardisation was a vital element in the growth of molecularisation more generally,[74] and facilitated the exchange of data, materials, and ideas within what we might call a "molecular economy".

Prusiner hitched his own scrapie research to the molecular biological bandwagon in the mid-1980s, when he began to look for the PrP gene. By 1989, when he began to manufacture transgenic mice, he was a keen proponent of molecular biological methods. DeArmond suggests that these transgenic experiments played a significant role in winning the support of other fellow scientists. He comments that with the transgenic model, Prusiner's group gained momentum.[75] Just after reporting Prusiner's success in transgenic experiments, *the New York Times* reported that the

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Infectious Process, Knowledge, Discourse, and Politics of Prions (San Francisco: University California Press)

[72]The molecular bandwagon is proposed with the case of cancer research by Joan Fujimura. For more details, see **Fujimura, Joan H.** (1988) 'The molecular biological bandwagon in cancer research: where social worlds meet', *Social Problems 35* (3): 361-283; **Fujimura, Joan H.** (1996) *Crafting Science: a sociohistory of the quest for the genetics of cancer* (Cambridge, Mass: Harvard University Press)

[73] **Fujimura, Joan H.** (1996) *op. cit.* note 72: 2

[74] **Sturdy, Steve** (1998) 'Reflections: molecularisation, standardization, and the history of science', Soraya de Chadarevian and Harmke Kamminga (eds) *Molecularising Biology and Medicine: new practices and alliances, 1910s-1970s* (Amsterdam: Harwood Academic Publishers): 287

once heretical theory had now gained huge credibility within the scientific community.[76] This view is borne out by useful study how use of the term prion proliferated in the scientific community. Carol Reeves identifies three different groups of scientists; (1) "exposed & infected" users, who agree with Prusiner and employ the term almost as aggressively as did Prusiner; (2) "exposed carriers", who remain uncertain or sceptical but employ the term; (3) "exposed & uninfected" users, who disagree with the prion idea and avoid using the term. According to Reeves' survey, there was a gradual increase in usage of the prion terminology.[77]

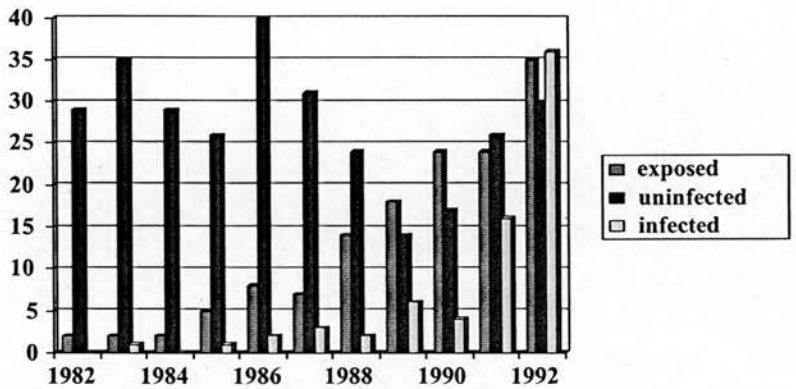

Table 3: Use of the term "prion" between 1982 and 1992
Note: Exposed, carriers = those who employ prion terms but are sceptical of prion theory; exposed, uninfected = disagree with prion theory and avoid prion language; exposed, infected = agree with prion theory an employ prion (Prusiner not author)[78]

However, as we can see in the Table 3, between 1990 and 1992 there was a remarkable increase of aggressive usage of prion. Between 1990 and 1992, the number of infected users increased remarkably. This coincides with the publication of the results of transgenic experiments on scrapie and other prion diseases that Prusiner and his team conducted between 1989 and 1992. In fact, before the transgenic experiment, Prusiner's position in the scientific community was still defensive, and many regarded his theory as heretical. By 1992, however, the whole map of the controversy had been changed, and the general mood of the disciplinary

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[75] **DeArmond, Stephen** (2000) *op. cit.* note 28

[76] **Blakeslee, Sandra** (1991) 'Heretic theory on brain diseases gains new ground', *New York Times* (8 October, 1991): C12

[77] **Reeves, Carol** (2002) *op. cit.* note 61: 115

[78] *Ibid.*

neighbours has come down on the side of prion theory. As such the transgenic technology played a pivotal role in persuading the disciplinary neighbours.

We can point to several reasons why Prusiner's participation in the molecular bandwagon won him the support of his disciplinary neighbours. In the first place, his use of transgenic mice aligned his scrapie investigations with what were widely seen to be cutting-edge developments in other areas of biomedicine. Prusiner's adoption of this new molecular biological technique, and its application to the elucidation of a puzzling but important family of diseases – hitherto called the unconventional slow viruses – helped to vindicate the investment that had been made in molecular biology by scientists from a wide range of biomedical disciplines. Consequently, many enthusiastic partisans of molecular biological and specially transgenic techniques as standardised research tools in bioscience were among those who praised Prusiner's transgenic mouse work.[79]

Conversely, scientists working in other fields such as Alzheimer's disease now attempted to apply Prusiner's idea about protein folding to their own research.[80] In part, this was presumably because Prusiner's innovative use of exciting new molecular biological techniques appeared to offer a possible way out of the stagnating programme of research into unconventional slow viruses and other supposedly similar neurodegenerative disorders. In part, too, the attractions of Prusiner's transgenic method seems to have been due to the possibility that it might open the way to a possible pharmaceutical solution for these diseases. It engaged directly with the interests of the pharmaceutical and commercial companies. Although supposed prion diseases are generally rare in humans, the pharmaceutical issue became more significant when the disease in sheep was shown to transmit into cattle in Britain. The outbreak of BSE (Bovine Spongiform Encephalopathy) alarmed scientists. The scientific community urgently needed to produce effective means of

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[79] **Sofroniew, M. V. and K. Staley** (1991) 'Transgenic modelling of neurodegenerative events gathers momentum', *Trends in Neuroscience 14*(12): 513-4; **Hardy, J.** (1991) 'Prion dimers: a deadly duo?', *Trends in Neuroscience 14*(10): 423-4.

[80] For example, there is a review paper concerning the search for a possible link between prion and the Alzheimer's [**Price, D. L., D. R. Borchelt, et al.** (1993) 'Alzheimer disease and the prion disorders amyloid beta-protein and prion protein amyloidoses', *PNAS* ***90*** (14): 6381-4];

intervening in this epidemic. Prusiner's experimental results with transgenic mice presaged a way to satisfy such demands by suggesting the possible development of molecular biological techniques of diagnosis and treatment. The pharmaceutical and biotechnology industries now came to see that their interests were involved. Since then, researchers in the prion group have rushed to set up commercial biotechnology companies to sell new methods of diagnosis and possible clinical solution by using their biotechnology. For instance, at least 35 laboratories are currently searching for commercial diagnostic and clinical possibilities in this field.[81] In particular, in 1997 some of Charles Weissmann's researchers have established a biotechnological company called "Prionics Inc." They have already commercialised two diagnostic methods: Prionics®-Check WESTERN and Prionics®-Check LIA. [82] Moreover, Prusiner's team attempted the first pharmacotherapeutic treatment of CJD in humans, although it was not successful.[83] The prion group's adoption standard biotechnological methods thus met the needs and expectations of wider groups of disciplinary neighbours, including the biotech industry. As a result, it played a role in strengthening the prion research group.

The sceptics, on the other hand, especially the Edinburgh researchers, continued to focus on classical genetic and pathological techniques such as measuring incubation period and pathological change. These techniques were calculated to engage the attention of the immediate scientific community, and played a part in building consensus during the 1960s and 1970s. However, once the molecularisation of biology came into play, such techniques were no longer fashionable and less likely to be the object of attention by the disciplinary neighbours. Sometimes, the lack of a

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there is also a journalistic review on the prospects of protein studies, see **Taubes, Gary** (1996) 'Misfolding the way to disease', *Science 271* (15 March 1996): 1493-1495.

[81] **The official mad cow disease home page** (http://www.mad-cow.org)

[82] The Prionics was established by one of Charles Weissmann's researchers, Bruno Oesch, at Zurich. For more information, see the website of Prionics Inc., http://www.prionics.ch

[83] This is the famous case of Rachel Fober who was a victim of new variant CJD, and who went to San Francisco for clinical treatment led by Prusiner and Korth. It had some success but the victim finally died later. **Dealler, Stephen** (2001) 'At long last, signs of a BSE breakthrough', *Guardian* (5th September 2001); **Brockes, Emma** (2002) 'To the last breath', *Guardian* (15th January 2001); **Korth, C., B.C.H. May, F.E. Cohen, S.B. Prusiner** (2001) 'Acridine and phenothiazine derivatives as pharmacotherapeutics for prion disease', *PNAS 98* (17): 9836-9841

molecular approach in the NPU was seriously considered by the members of the institute, and some attempted to recruit new molecular biologists. Before 1986, the NPU did not pursue any project using a biochemical and molecular biological approach. When Prusiner and his collaborative team produced significant experimental data on protein sequencing and found the prion gene in 1985, the NPU still did not respond. Even when they began to recognise a need for biochemical expertise, moreover they tended to think of it in classical genetic rather than molecular biological terms, as a statement from one of the NPU members reveals:

> Mr. Walker: [...] It may be that you can help on this question as well. If the biochemist had been in place earlier, would additional projects have been possible? [...]
> Dr. Hope: [...] Yes, certainly if we had had Nora's [Hunter who is a biochemist in NPU] expertise at the beginning of 1985, I think we would have been able to initiate the genetic linkage studies earlier.[84]

As a matter of fact, the leaders in the institute - Dickinson, Fraser, and Kimberlin - did not believe in the efficiency and reliability of the molecular biological approach. Because of their experience of biophysical research conducted at Compton during the 1960s, they were inclined to think that the molecular approach was a waste of resources.

7. Linkage of prion to social network

For twenty years, the opposed scientific programmes of the prion advocates and prion sceptics have competed and conflicted. However, equipoise in the controversy has gradually broken down, and the specialist programme of the prion group has gained the upper hand. This does not mean that the Prusiner's programme has an innate superiority. As seen, the two factions produced many valuable experimental data, but they failed to reach an agreement. Moreover, the prion controversy cannot be said to have reached closure. Rather, the voices of the prion sceptics, though insistent simply attract less attention than hitherto. Consequently, there is no point in attempting to explain this shift in opinion by pointing to some definitive piece of

empirical research or theoretical insight that resolved all the various points of disagreement between the two parties. Rather, we must look at the shifting networks of interconnected scientific interests that have determined the credibility of one or other group within the wider scientific community and beyond.

During the 1970s, the generalist biological approach was the dominant in scrapie research. It was successful in part because the small size of the research community enabled a handful of researchers in the early 1960s to establish a coherent agenda for collaborative research into the diseases. Thus, the primary task at the time was consolidation of the research network rather than expansion of the community. Based on generally accepted genetic and pathological methodologies, the generalist programme of Dickinson's group became a mainstream of the scrapie research community. Meanwhile, the failure of biochemical and biophysical work on scrapie shaped a general feeling of frustration with such approaches. As a result, in so far as the wider scientific community took an interest in scrapie research, it tended to regard the pathogenic studies of Edinburgh as definitive. Moreover, as we have seen, the continuity of the Edinburgh approach was underwritten by a degree of constancy of funding and job security that survived a series of reforms in the UK system of government research funding in the early 1970s.[85]

By the mid-1980s, this kind of stable research funding, and the long-term collaborative research programmes that it made possible, were becoming less and less the norm, even within the British system of research council funding. At NPU, the imposition of greater managerial controls over government scientists, and pressure for more commercially relevant lines of research, led Dickinson to resign in 1987, over fears that the autonomy of his unit was under threat.[86] Genetically oriented research on scrapie and BSE continued under Moira Bruce and others, but it

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[84] **Fraser, Hugh, Jean Manson, James Hope, Nora Hunter & Moira Bruce** (1999) 'Transcription of oral hearings: day 23', *The BSE Inquiry* (11 June 1998: The BSE Inquiry): 39

[85] See chapter 5, 'how controversy ends' and **Wright, Susan** (1994) *op. cit.* note 1

[86] **Biggs, Peter** (1998) 'Transcription of oral hearings: day 44', *The BSE Inquiry* (8 July 1998: The BSE Inquiry): 58-60

was increasingly integrated into a wider programme of research on animal diseases that tended to favour biochemical and molecular biological approaches.[87]

Meanwhile, in the US, government science policy was changing even more markedly in favour of the commercialisation of biomedicine. In 1980, the American Congress passed a law that university or federal research achievements, supported by federal funds, could be profited from personally.[88] The government thus changed their basic idea on public ownership of scientific research. After that, the commercialisation of the life science has accelerated. Commercial molecular biology was at the forefront of this process. The first biotechnology company, Cetus, had been established in 1975, and as early as 1978, the *Boston Globe* published a headline, "Clone business: it's growing fast. It's growing fast."[89] Interestingly, one of Prusiner's key collaborators, Charles Weissmann, is a frontrunner in the commercialisation of molecular biology. He was a founding member of the first biotech company in Europe, *Biogen,* in the late 1970s.[90] Another collaborator, Leroy Hood, also established a biotech company, the Institute for Systems Biology, in 1999.

Prusiner's market oriented and contractual style of practice thus corresponds closely to the kind of scientific activity favoured by policy makers and that is seen to

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[87] Jim Hope, who is a biochemist in NPU, became an acting director after the resignation of Alan Dickinson and Richard Kimberlin in 1988. Despite considerable efforts to find a new head of unit, no appointment was made. Finally, the head of the division of molecular biology in the Institute of Animal Health (IAH), Chris Bostock, who had been increasingly involved in developing the research strategy at the NPU, took overall charge of the unit in 1991. [**Institute of Animal Health** (1998) 'Research on transmissible spongiform encephalopathies, 1986-1998: an overview', *The BSE Inquiry: statement 105* (The BSE Inquiry: www.bse.org.uk/files/ws/s105.pdf): 3-4]. As a matter of fact, the NPU was set up for the purpose of unified research on the scrapie-like diseases in animals and humans. However, in the late 1980s, there was a huge demand to set up a new research institute for molecular biological research on the diseases, thus another unified research institute was established including NPU. This confusion and transformation of research strategy in the unit implies that the old autonomous non-standardised research came to an end, and the new biotechnological package was embraced and applied.

[88] The laws are the Bayh-Dole Act, and the Stevenson-Wydler Act in 1980, and the Federal Technology Transfer Act in 1986. For more detailed explanations about the context, see **Andrews, Lori, Dorothy Nelkin** (2001) *op. cit.* note 49: chapter 3 on the genetic gold rush.

[89] **Boston Globe** (1978) 'Clone business: it's growing fast. It's growing fast', *Boston Globe* (25th June 1978): 1

[90] Weissmann established the biotech company with two businessmen, Dan Adams, and Ray Schafer, and nine scientists including Walter Gilbert (Harvard) and Kenneth Murray (Edinburgh). [**Wright, Susan** (1994) *op. cit.* note 1: 87]

support some of the most commercially exciting developments in modern biomedicine. In a context of molecularisation, which includes commercialisation and standardisation of biomedical techniques increasingly large sections of the scientific community tend to inhabit and favour much the same kind of socio-economic circumstances as Prusiner inhabits – a world of short-term contracts, deals and patents etc. Meanwhile, though the prion sceptics might be doing worthy work, they are largely isolated from this new scientific culture. It is for this reason that their generalist biological programme has become less convincing and less interesting than the specialist molecular programme pursued by Prusiner. Prusiner's triumph in the prion controversy is ultimately due not to any inherent superiority of his theories or data, but to the peculiar scientific culture that tends to favour his entire way of doing science over that of his opponents.

8. Conclusion

In this chapter, I have sought to answer the two major questions about the prion controversy; how the controversy between the prion group and its sceptics was sustained for twenty years, and why the prion group has latterly gained much wider support from the scientific community. I have argued that the two factions of scientists pursued quite distinct styles of research programme. The fundamental difference between the prion group and prion sceptics derived from their divergent research priorities and methodologies, which I have characterised in terms of a generalist biological programme on the one hand and a specialist biochemist programme on the other hand. The prion sceptics adopted the former style, and the prion group adopted the latter. These divergent styles in turn embodied different aims, methodologies and experimental systems of research.

For the purpose of elucidating why such divergent programmes have been maintained, I have looked in particular at the material and social conditions of the two factions of scientists. These differ quite strikingly. Differences in funding system, especially, have played a significant role in sustaining the divergent programmes. On the one hand, the prion sceptics are generally working in secure posts in long-term

government-funded institutions. In these circumstances, they have been able to conduct long-term genetics-based biological research into the scrapie-like diseases. On the other hand, the prion group is located in a totally different situation: their projects are largely dependant on short-term grants, which tends to encourage the pursuit of more narrowly defined and self-contained research. This sharp difference in material condition can elucidate why the sceptics have tended to focus on a general understanding of the disease, whereas the prion group focuses specifically on the structure of the agent. Under the short-term grant system, it is not possible to launch a long-term biological project.

Furthermore, the two factions have sharp contrasts with regard to social order. For conducting their long-term general biological experiments, the sceptics developed what can be characterised as communitarian social relations. Their programme requires each participant to possess a general understanding of the whole process of their experiment, in order to conduct effective co-operative work with colleagues. These social relations are apparent in the degree of access to instruments of production and in the communal ownership of the products of research. By contrast, the prion group exhibits quite different social relations. The short-term competitive funding system leads them to maintain an individualistic and contractual social order. In this social order, advancement is a consequence of individual productivity. Consequently, the whole social structure of the laboratory is based on individual expertise; not every member is allowed to access to all of the experimental instruments, and the products of research also belong to individual researchers. This system encourages competition between researchers, and contractual relationship between collaborators.

Within those divergent material and social circumstances, the two factions of researchers maintained their own research programmes during the twenty-year controversy. Likewise, Prusiner's ultimate success in this controversy can be elucidated in terms of wider social and economical changes in biomedicine. The prion group conforms more closely than the prion sceptics to the way that many areas of biomedical science are changing. In particular, modern biomedicine tends increasingly towards commericalisation and standardisation, including individual

competitions, short-term contracts, and the use of standardised tools for research. This large-scale shift in biomedicine is often defined in terms of "molecularisation". The prion group is located at the forefront of shift, whereas the sceptics are largely isolated from it. Prusiner's programme is intimately linked into the wider social networks that are influential in determining how scientific funds and credit are distributed. The dominance of his prion theory is thus a consequence of the social and cultural position he occupies, and his ability, as a scientist, to fulfil the expectations that such a position brings with it.

Chapter 10 – Conclusion

At the start of this thesis, I set out to address two questions. Firstly, how scrapie researchers defined and redefined the mysterious disease from the 1960s when the first full-scale laboratory studies set up to the 1990s, when it came to be widely regarded as the exemplar of a prion disease. Secondly, I raised the question of the relationship between scrapie research and wider scientific and social developments. In this chapter, I pull together various threads of the discussion from the previous chapters.

1. How scientists defined and redefined the nature of scrapie?

This work began its analysis of early scrapie research between 1750 and 1960, with a brief discussion of the wider socio-economic context and the emergence of veterinary science in Britain (chapter 2). With this wider analysis as background, it described the foundation and development of scrapie research from observations by the gentry to the establishment of modern veterinary investigation in the twentieth century. During the 1940s and 1950s, scrapie research was mainly conducted in the Moredun research institute at Edinburgh. Then, in the 1950s, the ARC decided to set up new research programmes on scrapie in Edinburgh and Compton, England. With this institutionalisation of research on scrapie, knowledge of the disease was transformed: from being a local matter, embodied in the crafts and practices of local farmers and shepherds, it now came to be defined in the universalistic terms of laboratory science.

The first large-scale programmes of research into scrapie were conducted in Edinburgh in collaboration between the Moredun Institute and Animal Breeding Research Organisation (ABRO), and by the scrapie research group in the Institute for Research on Animal Diseases (IRAD) in Compton. During the 1960s, these two teams conducted various laboratory experiments that led them to put forward opposing speculations on the nature of the infectious agent at the end of the 1960s. These conflicting views caused disputes in the small scrapie research community. In

chapters 3 and 4, I described in detail the procedures of various experiments conducted in Edinburgh and Compton. Those conducted at the Moredun-ABRO unit were led by a geneticist, Alan Dickinson, who launched a full-scale genetic-pathological project to clarify the mechanisms of replication and pathogenesis. Over around 15 years, this genetic and pathological work revealed many notable characteristics of the agent. In particular, the researchers showed specific interactions to take place between the strain of the agent and the host genotype. They suggested that the mechanism of infection was quite different from conventional viruses, and argued that it should be attributed to a new type of infectious agent, a virino.

The Compton team drew a quite different picture (chapter 4). During the 1960s, several research groups in IRAD sought to characterise the agent by using conventional biochemical methods. However, they were not successful. In this context, David Haig and Tikvah Alper launched a new project to estimate the molecular size and weight of the agent using radiobiological methods. They found not only that the agent was very small, but also that it was resistant to UV irradiation. On the basis of these results, they speculated that the replication of the agent might occur without involving nucleic acids, by locating the scrapie agent in a self-replicating plasma membrane. This met with considerable criticism, because the conclusions implied deviation from the conventional wisdom of biology, the "central dogma". Furthermore, the conclusion of the work was also at variance with what Dickinson's group in Edinburgh had shown, namely, strain variation of the agent. The two ideas were the subject of controversy during the 1970s, and no consensus was reached. The dispute between the two groups intensified, and they failed to find a common ground from which to consider their respective findings.

The confrontation was not only centred on divergent experimental results, but was also exacerbated by competitive relations between the two research groups. Moreover, the highly individualised and competitive character of work at IRAD, which encouraged the researchers to make bold claims, was at odds with the more collaborative work at the Moredun-ABRO unit, which led the researchers to make more cautious speculations based on a wider range of biological considerations. The controversy ended with the dramatic intervention of the ARC, an administrative and

funding body, which sided with the Edinburgh researchers and terminated the scrapie programme at Compton.

In the American context, by contrast scrapie research was not major issue in veterinary science during the 1960s, and 1970s. Although there were some research groups interested in the disease in its own right, most interest in scrapie derived from concern with human neurological diseases such as kuru and CJD (chapter 6). During the 1970s, most researchers in America accepted a loosely defined concept of scrapie as an "unconventional slow virus", as did the groups of researchers studying kuru and CJD. This convergence enabled the different groups to forge collegial links with other scientists and to make claims for the importance of their collective endeavour. This convergence around the concept of unconventional slow viruses was followed by a significant degree of methodological convergence, notably around scrapie as a convenient laboratory model of the whole family of diseases. At the local level, researchers came increasingly to share standardised methods of purification and chemical treatments to isolate the putative agent of scrapie.

With this increasing standardisation, a neurologist in University of California, San Francisco, Stanley Prusiner, set up his own research programme to purify the agent in the early 1970s (chapter 7). During the early years, Prusiner attempted to purify the agent by using the centrifugation method, and achieved a partially purified form of the agent. He also developed a new faster and more economical bioassay technique with the hamster model of scrapie. This in turn enabled him to test the effects of a wide range of chemicals on his partially purified scrapie agent in a very short time, and to produce a considerable amount of biochemical data. On the basis of those experimental data Prusiner produced a high-profile publication in *Science* in 1982 in which he put forward quite striking evidence for the involvement of protein in scrapie infectivity, and an equally striking failure to find evidence of the involvement of nucleic acids. This high profile publication also provided him with a platform from which to suggest that scrapie represents a new category of infectious agent for which he proposed the name "prion".

Prusiner's suggestion of the prion hypothesis caused a twenty-year controversy in the scientific community. Many people thought that his idea of prions implied that

they might be devoid of nucleic acids. This was clearly an unorthodox approach because it was a violation of the biological principle that biological information must be encoded in a nucleic acid molecule. The controversy divided the community of scrapie research into two: the prion group and its sceptics (chapter 8). During the 1980s and 1990s, both factions of scientists produced many interesting experimental results. However, attempts to discover the nature of the scrapie agent have been inconclusive, although the weight of opinion amongst scientists has increasingly come down on the side of Prusiner's prion theory. Over the past twenty years Prusiner has gained considerable scientific credibility from fellow scientists. Correspondingly, his opponents, the prion sceptics, who were once the mainstream in this field, have been marginalized. Nevertheless, the sceptics continue to pursue their research project to prove their own theory that the scrapie agent contains a nucleic acid genome-like informational molecule.

2. How social circumstances played a role in defining the nature of scrapie?

A laboratory is a microcosm of society. Scientific practice in a laboratory cannot be fully accounted for without acknowledging the various social and cultural dimensions of scientific activity. As I have shown in chapter 5, the early dispute over the nature of the infectious agent was sustained in part by the existence of two distinctive laboratory cultures. Each group of researchers had different goals and traditions of research. In this context, they failed to find common ground during the controversy. In this case, two cultural styles were in conflict, and this escalated the intensity of the controversy between scientists. Throughout the controversy, however Edinburgh succeeded in producing knowledge that conformed more closely to views held elsewhere in the scientific community. Eventually, the dispute, which looked as though it was heading for endless confrontation, was brought to an end in Edinburgh's favour with the intervention of the ARC, an administrative body.

The case of the prion controversy also shows how different social and cultural factors played an important role in sustaining divergent scientific

programmes at least for twenty years (chapter 9). I have argued that the two factions of scientists pursued quite distinct styles of research programme. The fundamental difference between the prion group and prion sceptics derived from their divergent research priorities and methodologies, which I have characterised in terms of a generalist biological programme on the one hand and a specialist biochemical/molecular biological programme on the other hand. Also, I have looked at the material and social conditions under which the two factions of scientists worked. Differences in funding arrangements, especially, played a significant role in sustaining the divergent programmes. On the one hand, the prion sceptics were generally working in secure posts in long-term government-funded institutions. In these circumstances, they were able to conduct long-term genetics-based biological research into the scrapie-like diseases. On the other hand, the prion group operated under quite different circumstances; their projects were largely dependent on short-term grants, which tend to encourage the pursuit of more narrowly defined and self-contained research. This sharp difference in material conditions can help to explain why the sceptics tended to focus on a general understanding of the disease, whereas the prion group focused specifically on the structure of the agent. Under the short-term grant system, it was not possible to launch a long-term biological project.

Furthermore, the two factions show sharp contrasts with regard to their internal social order. For conducting their long-term general biological experiments, the sceptics developed what can be characterised as communitarian social relations. Their programme required each participant to possess a general understanding of the overall process of their experiments, in order to conduct effective co-operative work with colleagues. These social relations are apparent in the degree of shared access to the instruments of production and in the communal ownership of the products of research. By contrast, the prion group exhibited quite different social relations. The short-term competitive funding system led them to maintain an individualistic and contractual social order. In this social order, advancement is a consequence of individual productivity. Consequently, the whole social structure of the laboratory is based on individual expertise; not all members are allowed to access

to all of the experimental instruments, and the products of research also belong to individual researchers. This system encourages competition between researchers, and contractual relationship between collaborators.

A few words must be said about why the prion theory has lately come to be favoured by fellow scientists and public (chapter 9). Prusiner's ultimate success in this controversy can be elucidated in terms of wider social and economic changes in biomedicine. The organisation and practice of the prion group conforms more closely than the prion sceptics to the way that many areas of biomedical science are changing. In particular, modern biomedicine tends increasingly towards commericalisation and standardisation, including individual competitions, short-term contracts, and the use of standardised tools for research. This large-scale shift in biomedicine is often defined in terms of "molecularisation". The prion group is located at the forefront of this shift, whereas the sceptics are largely isolated from it. Prusiner's programme is closely linked into the wider social networks that are influential in determining how scientific funds and credit are distributed. Therefore, the dominance of his prion theory can be said to be a consequence of the social and cultural position he occupies, and his ability, as a scientist, to fulfil the expectations that such a position brings with it. While Prusiner himself declares of the whole controversy that "the saga of prions truly represents the triumph of scientific investigation over prejudice",[1] I would like to rephrase this to suggest that "the saga of prions truly represents the triumph of a specialist biochemical/molecular biological programme over a general biological programme".

[1] **Prusiner, Stanley** (1999) *Prion Biology and Diseases* (Cold Spring Harbor: Cold Spring Harbor Laboratory Press): v

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